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Neuroplasticity in Neuro-oncology: Neuropsychological and neuroimaging correlates of brain tumors

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Prof. ***Carlo Semenza*** *supervised my research work during the whole period of Ph.D. Since my master degree, when my professional way with him begun, and ever since, he has always got an answer whenever I asked.*

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Introduction

Brain tumors are a rare disease, however the cost in term of unfavorable prognosis and impact on quality of life is very high. The complex treatment requested by a brain tumor (surgery and pharmacological therapy) may determine neurological and cognitive consequences, that need an immediate and precise intervention. For this reason, novel diagnostic methods that combine behavioral and imaging data are requested. This research work was aimed at investigating cognitive and imaging correlates of brain tumors and is built on different aims.

The first goal was the definition of the neuropsychological profile of brain tumors. We specifically focused on cognitive deficits associated with the pathophysiology of the tumor. In other words, we investigated if brain tumors may cause a specific type of cognitive damage, based on the specific pathophysiological behavior in affecting the brain. To this end, an observational study was designed and the assessment of a cohort of brain tumor patients in the pre-operative stage was performed. By means of an extensive neuropsychological protocol, patients were evaluated in different cognitive domains. This study allows us to describe the cognitive features of the tumors, by taking into account some physiological variables: type of tumor (e.g. glioma vs meningioma), site of the lesion, extension of the lesion.

To the best of our knowledge, no study so far has defined the cognitive profile of brain tumors taking in account the specific neurological nature of this pathology, in order to define a suitable neuropsychological battery for the cognitive characterization of brain tumors. The second aim concerned precisely the effort to define the specificity of the neuropsychological battery in detecting the particular cognitive disease consequent to brain tumors. To achieve this goal, we compared the neuropsychological performance of the group of patients with brain tumor with a group of patients with focal stroke, a neurological disorder involving a very different pathophysiological process. This implies the identification of the neuropsychological tests that are sensitive in detecting the specific as well as subtle cognitive deficits consequent to brain tumors.

The third aim had a longitudinal perspective and concerned the study of the effects of tumor resection on cognitive functions in the long term. To achieve this goal, we analyzed the behavioral data of the group of patients at three different time points: pre-surgical, post-surgical and one month follow-up. We expected a global worsening of the cognitive scores in the immediate post-operative stage, with a subsequent recovery at one month follow-up. A preliminary study was also conducted in order to define the effect of the treatment (radiotherapy and chemotherapy) on cognitive functions, with the aim to clarify the interaction of surgery and treatment in affecting the brain. Hence a further follow-up was also conducted four months from the neurosurgery and after the therapy. Importantly, this study clarified the interaction between the cognitive effects of the treatment and surgical intervention. Furthermore, it shed light on the relevance of follow-up neuropsychological assessment in monitoring brain tumors.

The present doctoral thesis aimed at clarifying the contribution of neuropsychological as well as neuroimaging measures in order to better characterize the specific pathophysiological processes beneath functional and cognitive symptoms. For this reason, a further effort consisted in exploring structural and functional neuroimaging biomarkers able to predict the patient's quality of life after tumor surgical resection. We furthermore aimed to assess the added value of the use of local and global brain connectivity in the clinical decision process. To this end, together with the neuropsychological evaluation, metabolism and perfusion data were longitudinally acquired, using simultaneous dynamic PET and MRI techniques. These data were acquired before surgery, after one month, and after three months from surgery. This study is still ongoing.

The overarching goal in the long term of the whole research is to take into account together neuroplasticity and neuropsychological aspects in neuro-oncology in order to create a new way of taking care of patients with brain tumor. Of note, the correlation between tumor variables, behavioral outcome and structural, functional, and metabolic metrics of brain organization allows individualized planning of surgery and treatment. This planning will therefore be tailored considering the characteristics of the single patient, leading to a better outcome and a reduced impact on functions and quality of life.

Part 1: Introduction to brain tumors

Chapter 1

Pathophysiology of brain tumors

1.1 Classification

Brain tumor is defined as an abnormal cell formation within the cerebral tissue or the structures surrounding it. It is possible to distinguish two main types of tumors: malignant tumors and benign tumors. Malignant tumors can be divided into primary tumors, which start within the brain tissue, and secondary tumors (brain metastasis), which originate from another part of the body. In 2016 the WHO introduced a new classification of brain tumors which represents a real innovation of the previous classifications, entirely based on the concept of histogenesis, that is the microscopic similarity of the tumor cells with the presumed cells of origin. The new WHO classification instead is based, for the first time, on molecular parameters in addition to histology (Louis et al., 2016). This innovation is hoped to lead to a better diagnostic accuracy, with a consequent advantage in determinations of prognosis and in treatment planning. Among the several novelties of this new classification, one of the most important is a major restructuring of the diffuse gliomas and other embryonal tumors, incorporating new entities defined by both histology and molecular features, such as the differentiation between glioblastoma IDH-wild type and glioblastoma IDH-mutant. The 2016 edition has added newly recognized neoplasms and has deleted some entities that no longer have diagnostic relevance.

Based on histology, we can distinguish the following classes of primary brain tumors:

- Gliomas, the most frequent kind of primary brain tumor, which derive from glia cells and are divided in astrocytomas, oligodendrogliomas, ependymomas and other rarer types
- Meningiomas, a typically benign tumor arising from ectodermal structures

- Primitive neuroectodermal tumors, that derived from precursor neuronal elements, such as neuroblastoma, medulloblastoma, ependymoblastoma, pineoblastoma
- Tumors derived from endocrine elements, such as pituitary tumors or pineal tumors
- Tumors of nerves or nerve sheaths (neuroma, schwannoma, neurofibroma)
- Primary Central Nervous System Lymphoma, derived from lymphocytes

Grading is another important concept in classifying tumor aggressiveness and commonly occurs on a 4 point scale (I-IV) created by the World Health Organization in 1993 (Table 1.1). The definition of the severity of a tumor is based on these characteristics:

- rate of growing
- infiltrative behavior
- tendency to relapse
- tendency to metastasize

Grade I tumors are the least severe and commonly associated with long term survival, with severity and prognosis worsening as the grade increases. Low grade tumors are often benign, while higher grades are aggressively malignant or metastatic. The histologic grade may vary from site to site within a tumor and it is common for sites of low-grade astrocytoma and glioblastoma to coexist, in some high-grade tumors there are even sites of well-differentiated astrocytoma.

Grading	Features	Subtypes
I	Slow-growing benign tumor, not infiltrative in surrounding tissue	pilocytic astrocytoma subependymal giant cell astrocytoma protoplasmic astrocytoma ganglioglioma xanthomatous astrocytoma subependymoma
II	Low grade malignant tumor, slow-growing but potentially infiltrative. Tendency to relapse after the treatment	fibrillary astrocytoma ependymoma oligodendroglioma mixed oligo-astrocytoma optic nerve glioma
III	Fast-growing malignant tumor, infiltrative in surrounding tissue, high tendency to relapse after the treatment with an higher grade	anaplastic astrocytoma anaplastic oligodendroglioma anaplastic mixed glioma
IV	Very fast-growing malignant tumor, infiltrative and aggressive	glioblastoma multiforme gliosarcoma gliomatosis cerebri

Table 1.1: Classification of tumor severity based on grading (I-IV, WHO 1993)

1.2 Epidemiology

Brain tumors are a rare disease, and account for only 2% of all tumors. 85% are primary cerebral neoplasms, while 15% are metastases especially from cancers in the lung, breast, kidney, gastrointestinal tract and skin (De Robles et al., 2015). The most common types of primary tumors in adults are meningiomas (usually benign) and glioblastomas.

The age-adjusted incidence rates of brain tumors tend to be highest in high-income countries. In Western Europe, North America, and Australia, there are about 6-11 new cases of primary intracranial tumors (including meningiomas) per 100.000 population per year in men and 4-11 new cases in women. The lower incidence in developing countries may be partly due to under-ascertainment, but ethnic differences in susceptibility to development of brain tumors cannot be excluded. Caucasians are more frequently affected than people of African or Asian origin.

In North America, Western Europe, and Australia, the mortality rates from brain tumors in 2009 were approximately 4-7 per 100.000 persons per year in men and 3-5 per 100.000 in women, meaning that in most geographical areas mortality rates were

similar to incidence rates. Survival of glioma patients is still poor, with the exception of pilocytic astrocytoma.

1.3 Clinical onset features

Intracranial neoplasms are essentially slow-growing masses and therefore most of their symptomatology is due to endocranial hypertension, with cephalalgia, nausea, vomit, papilledema. The headache is classically worse in the morning and goes away with vomiting. Onset often happens with focal epileptic crises whose nature depend on the localization of the tumor; also generalized crises may happen if the tumor involves the thalamus. Besides these hyperactivation symptoms, there can also be focal deficits: hemiparesis/hemiplegia if the tumor compresses the motor cortex, visual impairment in occipital tumors, and so on.

Unfortunately, often onset of a brain tumor happens late in its development and patients usually underestimate vague symptoms like headaches or personality changes, leading to diagnosis when they are already at an advanced stage.

1.4 Diagnosis

Brain tumors are often diagnosed occasionally because of brain imaging carried out for other reasons. It may be suspected in the presence of typical symptoms or an altered neurological exam. Neuroimaging remains the gold standard instrument for tumor diagnosis: CT might suggest the presence of a mass, but MRI with contrast is more specific and can better visualize the type of tissue and how it infiltrates normal brain matter. Furthermore, a number of specialized MRI scan components, such as functional MRI, perfusion MRI and magnetic resonance spectroscopy, may help to better characterize the structural features and the biologic behavior of the tumor (Castellano and Falini, 2016). A PET scan can also be performed to evaluate the proliferating activity of neoplastic cells. The result is confirmed by a biopsy, that can be performed using a needle if the mass is easily approachable, otherwise it can be done during an operation. For brain tumors is hard to reach or very sensitive areas, a stereotactic needle biopsy may be performed. Molecular testing can be carried out on tumor tissue to evaluate which type of therapy will be more effective.

1.5 Treatment

Surgery

Treatment depends on the type, size and location of the tumor. If the mass is accessible, surgery will be the main approach. The main aim of surgery is to remove as many tumor cells as possible, minimizing functional consequences. If the tumor is localized and easily separable from the surrounding tissue it can be totally removed, but in some cases access to the tumor is impossible and impedes or prohibits surgery. In some cases, imaging measures are not sufficient to distinguish between brain areas which are essential for some functions (language or movement) and areas which are removable without causing a dramatic loss of functionality. Therefore, the surgical resection is conducted with intraoperative monitoring procedures, that allow to check during the surgery if a particular area subtends a particular function (Duffau, 2004; 2005). Several current research studies aim to improve the surgical removal of brain tumors by labeling tumor cells with 5-aminolevulinic acid that causes them to fluoresce. Many meningiomas, with the exception of some tumors located at the skull base, can be successfully removed surgically.

Radiotherapy

Radiotherapy and chemotherapy can be used as adjuvants in tumors which could not be totally removed or as palliatives in high grade inoperable tumors. Radiotherapy may also be administered in cases of low-grade gliomas when a significant tumor reduction could not be achieved surgically. The goal of radiation therapy is to kill tumor cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy, multiple treatments of standard-dose fractions of radiation are applied to the brain. This process is repeated for a total of 10 to 30 treatments, depending on the type of tumor. Radiosurgery is a treatment method that uses computerized calculations to focus radiation at the site of the tumor while minimizing the radiation dose to the surrounding brain. Targeted drug therapies are available for specific kinds of tumor and are still being developed. The effectiveness of the treatment is evaluated with imaging methods.

Chemotherapy

Patients undergoing chemotherapy are administered drugs designed to kill tumor cells. The toxicity and many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumors puts this treatment further down the line of treatment options with surgery and radiation therapy preferred. Genetic mutations have significant effects on the effectiveness of chemotherapy. Gliomas with IDH1 or IDH2 mutations respond better to chemotherapy than those without the mutation. Loss of chromosome arms 1p and 19q also indicate better response to chemoradiation (Iv et al., 2018).

1.6 Pathophysiology

The effects of neoplasms on the brain are basically of three types: tissue infiltration, tissue compression and obstruction of CSF circulation (which causes hydrocephalus). Compression and infiltration clinically translate in irritation of brain tissue, which causes epileptic crises, and focal neurological deficits. The severity and rapidity by which these events take place depend on the nature of the tumor. For instance, high grade gliomas lead to local derangement of nervous structures which translate in a rapid onset of neurological deficits, while meningiomas have a slow growing rate and so symptoms may manifest only after years of disease. Compression by meningiomas also leads to circulation slowdown and thus to venous congestion, which in turn leads to interstitial liquid extravasation and cerebral edema, whilst in gliomas there is substance release which produces vasogenic edema. Tumors that occupy or compress the ventricles or the cerebral aqueduct determine hydrocephalus, which usually produces the signs and symptoms of intracranial hypertension rather quickly.

Gliomas comprehend the major categories of astrocytomas, oligodendrogliomas and ependymomas, which are then subcategorized in grades I, II, III and IV (WHO classification).

- Grade II astrocytomas, which constitute 25-30% of cerebral gliomas, may occur anywhere in the brain or spinal cord. Cerebral astrocytoma is a slowly growing tumor of infiltrative character with a tendency in some cases to form large cavities or pseudocysts. The tumor may distort the lateral and third ventricles and displace

adjacent cerebral vessels. In about two-thirds of patients with astrocytoma, the first symptom is a focal or generalized seizure, and 60-75% of patients have recurrent seizures in the course of their illness. Other subtle cerebral symptoms follow after months, sometimes after years. Headaches and signs of increased intracranial pressure are relatively late occurrences.

- Anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV) account for approximately 20% of all intracranial tumors and for more than 80% of gliomas in adults. Most arise in the deep white matter as heterogenous masses and quickly and extensively infiltrate the brain, sometimes gaining enormous sizes before attracting medical attention. The tumor may extend to the meningeal surface or the ventricular wall. On imaging it usually appears as an inhomogeneous mass surrounded by non-enhancing edematous brain tissue, consisting of a combination of infiltrating tumor cells and vasogenic edema.
- Oligodendrogliomas are mostly indistinguishable from other gliomas and up to half are mixed oligoastrocytomas. The typical oligodendroglioma grows slowly. As with astrocytomas, the first symptom is usually a focal or generalized seizure; seizures often persist for many years before other symptoms develop. Ependymomas account for approximately 6% of all intracranial gliomas and are derived from ependymal cells, the cells lining the ventricles of the brain and the central canal of the spinal cord. Clinically, cerebral ependymomas generally resemble the other gliomas.

Meningiomas represent approximately 15% of all primary intracranial tumors and originate from the dura mater or arachnoid. Grossly, the tumor is firm and sharply circumscribed, taking the shape of the space in which it grows. It may indent the brain and acquire a pia-arachnoid covering as part of its capsule, but it is clearly demarcated from the brain tissue except in the unusual circumstance of a malignant invasive meningioma. Infrequently, it arises from arachnoidal cells within the choroid plexus, forming an intraventricular meningioma. Meningiomas occur at sites of dural folds: 90% are supratentorial, and the majority of the infratentorial ones occur at the cerebellopontine angle. Small meningiomas (<2cm) are often found at autopsy in middle-aged and elderly people without having caused symptoms; they manifest

themselves only when they exceed a certain size and indent the brain or cause a seizure. The size that must be reached before symptoms appear varies with the size of the space in which the tumor grows and the surrounding anatomic arrangements: focal seizures are an early sign of meningiomas that overlie the brain; parasagittal frontoparietal meningioma may cause a slowly progressive spastic weakness or numbness of one leg and later of both legs, and incontinence in the late stages; sylvian tumors manifest themselves with a variety of motor, sensory, and aphasic disturbances in accord with their location, and seizures.

1.7 Genetic aspects

As argued above, in 2016 the WHO restructured brain tumor classifications including distinct genetic mutations that have been useful in differentiating tumor types, prognoses, and treatment responses. Recently, tumor molecular markers have been identified as better predictor of growth kinetics than classical histology. Genetic mutations are typically detected via immunohistochemistry, a technique that visualizes the presence or absence of a targeted protein. In particular, the genetic mutation introduced in the 2016 edition con be summarized as follow:

- Low grade gliomas are characterized by mutations in IDH1 and IDH2 genes
- Oligodendroglioma is distinguished by loss of both IDH genes combined with loss of chromosome arms 1p and 19q
- Astrocytomas is defined by loss of TP53 and ATRX
- Genes EFGR, TERT and PTEN are commonly altered in gliomas and are useful in differentiating tumor grade and biology

In particular, the isocitrate dehydrogenase 1 (IDH1) gene has an important role in the new WHO classification. More specifically, patients with mutation of the IDH1 (about the 30% of total gliomas) exhibit a survival benefit over patients with the wild type tumor, independent of age and histologic grading (Hartmann et al., 2013; Cheng et al., 2013). Such differences probably reflect growth characteristics that are typical of IDH1 subtypes. In fact mutant gliomas have a more diffuse pattern of growth and slower rate of cell proliferation, both aspects that are associated with better prognosis (Hodges et al., 2013; Baldock et al., 2014). The specific type of tumor proliferation and

the invasion characteristics of a specific tumor is called lesion momentum. The lower lesion momentum of tumors with IDH1 mutation may create a neural environment favorable for neuroplasticity. On the other hand the rapid proliferation typical of IDH1 wild type tumors does not allow a reorganization of brain tissue.

Chapter 2

Neuropsychological correlates of brain tumors

If we look at the natural progression of a brain tumor we can find different stages in which cognitive dysfunctions become a relevant problem, that cannot be neglected (Ali et al., 2018):

- the tumor itself
- the surgical resection
- the treatment (radiotherapy and chemotherapy)

These variables represent all a potential source of cognitive dysfunction. The pattern and severity of cognitive impairment varies greatly between individuals and depends on several clinical and demographic variables. In the effort of defining the cognitive profile of brain tumor patients it is necessary to take into account some pathophysiological aspects, that is histological profile, disease progression, treatment-related neurotoxicity and co-morbidities. Specifically, the nature of cognitive impairment depends on several factors including tumor grade, location, and size. Furthermore, tumors are frequently diagnosed at an advanced stage when they cause epilepsy, signs of intracranial hypertension or neurological deficits, which then might overshadow more subtle cognitive deficits (Taphoorn et al., 2004). About the onset and the progression of cognitive dysfunction, usually mental slowing with prominent executive and memory impairment mark the advanced phases of disease, whereas normal cognitive performance or subtle behavioral symptoms characterize the early disease course, irrespective of tumor location. Neuropsychological assessment may reveal brain damage in otherwise neurologically normal patients (Giovagnoli, 2012).

2.1 Neuropsychological intervention

A good neuropsychological assessment should be combined with the traditional neurological examination in order to precisely measure the amount of cognitive damage in association with the motor or sensory deficits (Papagno et al., 2012). In the early stage the assessment may help to characterize the effects of the tumor in patients with no other neurological symptoms. After treatment, cognitive evaluation gives indications for monitoring post-surgical changes and the effects of treatment (Armstrong et al., 2003; Ali et al., 2018). Neuropsychological testing may also contribute to quality of life assessment (Giovagnoli et al., 2005; Giovagnoli et al., 2012), or anticipate tumor recurrence by weeks or months (Armstrong et al., 2003; Meyers et al., 2003; Brown et al., 2006). According to the reasons given above, the cognitive assessment should be introduced in clinical practice as a routine exam, and also conducted at every stage of the disease, with different aims:

- *Pre-surgical assessment*: it allows to identify the specific nature and severity of cognitive damages caused by the tumor itself.
- *Intra-operative monitoring*: in some cases, to monitor cognitive functions during surgery allows to extend as much as possible the resection of the tumor minimizing the impact on functions, by identifying eloquent areas.
- *Post-surgical assessment*: if conducted in the immediate post-operative stage (within one week), it allows to quantify the impact of surgical resection on cognitive functions. A directly comparison between the pre and post cognitive performance leads to a discrimination between the effects of the tumor and the effects of the surgical procedure. It also yields information for planning non-pharmacological treatment, such as neuropsychological rehabilitation or psychological support.
- *Follow-up assessment*: if repeated at different time points from the surgery, it allows to monitor over time the condition of the patient, to evaluate the effectiveness of the possible neuropsychological rehabilitation, and to reveal new recurrence.

- *Neuropsychological rehabilitation*: if the assessment reveals cognitive damage in one of the stages of the disease, it is possible to schedule a rehabilitation program (see Bergo et al., 2016 for a review).

Regarding the neuropsychological assessment, the incompleteness of a single screening test and the necessity of an extensive evaluation is acknowledged (Robinson et al., 2015). However, there is no agreement about the tests that are more sensitive in evaluating the cognitive consequences of brain tumors, because of the large variability in the prevalence of cognitive deficits due to the wide variety of factors that may influence the expression of symptoms, as largely discussed above. The criteria commonly used to select cognitive tests are listed in table 2.1 (Giovagnoli et al. 2012). The literature provides some recommendations for clinical evaluation:

- multidimensional testing is necessary to characterized the complex cognitive pattern caused by a brain tumor.
- the test measures should be sensitive to detect clinically significant changes with practical consequence on everyday activities, but not time-consuming.
- compare the cognitive pattern with neurological signs and patients' report.
- a stepwise evaluation is recommended, from brief screening testing to detailed examination of specific cognitive deficits.
- cognitive testing should be routinely associated with quality of life evaluation in order to measure the impact of cognitive deficits on everyday life.

Currently, extensive neuropsychological evaluation is considered the gold standard for assessment cognitive disease resulting from brain tumor (Papagno et al., 2012; Ali et al., 2018). Giovagnoli (2012) summarized the most sensitive tests used in multidimensional studies (Table 2.1-2.2).

Selection criteria of neuropsychological tests
Type and frequency of cognitive impairment
Clinical and research purposes
Disease burden
Patient awareness, fatigability, compliance
Adequate psychometric properties
Ability to detect clinically significant deficits
Congruence with patients reports, everyday activities and quality of life
Staff burden

Table 2.1: Selection criteria of neuropsychological tests in evaluating brain tumor patients (Giovagnoli et al., 2012)

Test	Cognitive function
Trail making test, digit-symbol association, Corsi blocks span	Visuomotor coordination speed, set shifting, working memory
Stroop color-word test, attentive matrices	Divided attention, interference control
Grooved pegboard	Motor speed and dexterity
Raven colored progressive matrices, Wisconsin card sorting test	Abstraction, set shifting
Word fluency, semantic and phonetic, design fluency	Initiative, fluency
Rey complex figure recall, short story recall	Episodic memory
California verbal learning test, Rey auditory learning test	Learning
Mini mental state examination	Global cognitive profile

Table 2.2: Cognitive tests most frequently used in evaluating brain tumor patients (adapted from Giovagnoli et al., 2012)

2.2 Cognitive effects of brain tumors

Several variables should be taken in account that influence the manifestation of cognitive deficits: more likely, a combination of these factors contributes to cognitive dysfunction:

- **Tumor volume:** tumor volume has been found to be a strong predictor: high volumes have been associated to poorer performance in perceptual speed, executive function, memory and verbal fluency. This negative correlation between tumor volume and preoperative cognitive performance suggests that with increasing tumor volume normal brain tissue and its network connections are displaced or disrupted (Habets et al., 2014; Satoer et al., 2014; Dallabona et al., 2017).

- **Tumor location:** the specific site of the tumor in the brain influences the behavioral outcome. Frontal lobe and dominant hemisphere localization are significantly associated with worse performance on multiple neurocognitive tasks, especially language and executive functions. Patients with tumors in the dominant hemisphere tend to have more cognitive deficits at pre-operative stage than those with a tumor in the non-dominant hemisphere (Dallabona et al., 2017). Temporal lobe gliomas usually cause impairment in the domains of verbal learning, memory and language (Noll et al., 2016). Frontal lobe lesions can present also with behavioral and emotional changes.
- **Histology:** different types of tumor affect in different ways the brain tissue and may lead to different type of cognitive disease.
- **Connectivity:** the functions of the area where the tumor is located may be preserved, whereas the homologue area in the opposite hemisphere may be damaged, because of alterations in brain connectivity.
- **Rate of growing:** slow growing tumors produce primarily alterations in personality or mood, whereas rapidly growing tumors produce deficits on cognitive functions (Ali et al., 2018). Furthermore, in slow-growing tumors compensation and substitution neural mechanisms tend to mask focal deficits.
- **Genetic:** tumor genetic factors are believed to affect cognitive functions in glioma patients, both at the time of diagnosis and in response to treatment (Wefel et al., 2016; Kesler et al., 2017). Lesion momentum of the tumor impacts cognitive impairment, patients with wild type malignant glioma show greater cognitive dysfunction compared to IDH1 mutant patients. This is true independently from the location and the extension of the lesion. Furthermore, larger lesion size was associated with worse cognition only in patients with wild type tumors. The authors concluded that the severity of the cognitive impairment in patients with wild type form may relate to reduce neuroplasticity consequent to the grater lesion momentum characteristic of this molecular variant of glioma (Wefel et al., 2016).
- **Overall mass effect:** the volume of the surrounding edema summed to the volume of the tumor itself has been demonstrated to have an impact on pre-operative cognitive performance, in different cognitive domains (Dallabona et al., 2017).

- **Comorbidity:** hydrocephalus and epileptic seizures are often associated with brain tumor and can causes cognitive symptoms as well.

2.3 Impact of neurosurgery on cognitive functions

It is well known that neurosurgery is the gold standard treatment of tumors and the main aim of this procedure is to maximize the extension of resection while preserving brain functions. Indeed, neurosurgical procedure can have some negative effects on cognition. The effect depends on three main factors and their mutual interaction: the extension of the resection, the site of tumor in the brain (if the tumor is localized in an eloquent area), the time elapsed since the surgery itself.

2.4 Effects of pharmacological treatment on cognitive functions

Investigations of the effects of radiation on neuropsychological functions have revealed variable outcomes, ranging from no effect to severe cognitive impairment. Specifically, radiation-induced cognitive impairment has been reported to occur in 27-90% of adult patients with brain tumors (Meyers et al., 2006). Conventionally, the effects of the radiotherapy are usually divided into three groups:

- acute effects, that occur immediately after the radiation up to six weeks
- early delayed effects, that occur up to six months after radiotherapy
- late effects, that occur at least six months after the radiation

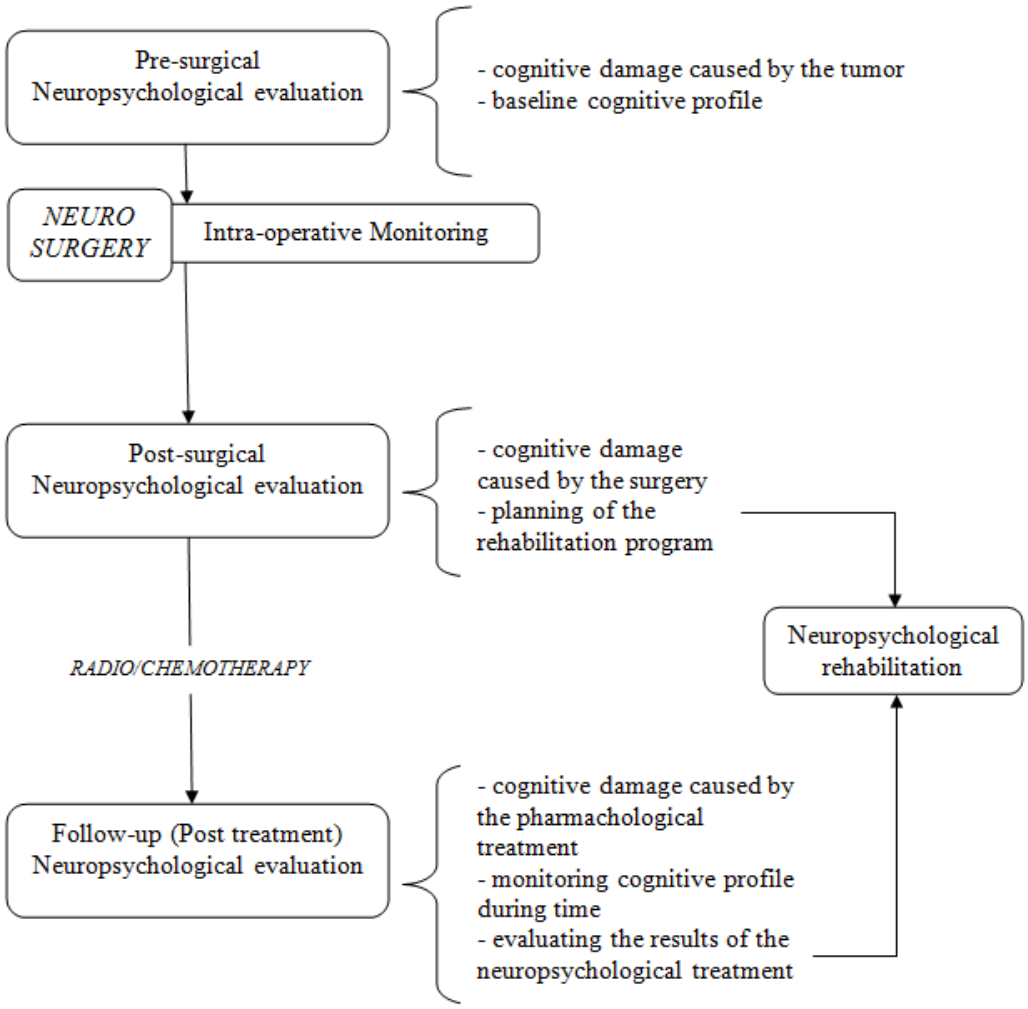
Unlike early effects, late effects are often irreversible.

After treatment, neuropsychological assessment rarely reveals focal cognitive symptoms, but more likely identifies a non-localized cognitive pattern, characterized by mental slowing, poor psychomotor coordination, frontal behavior, personality change and memory weakness (Taphoorn et al., 2004; Costello et al., 2004; Armstrong et al., 2012; Ali et al., 2018). The low-grade and high-grade brain tumor groups showed a differential pattern of performance following radiotherapy, with the low-grade tumor performance more preserved in all neuropsychological domains. Their pattern of improvement was very similar to that of the nonmalignant brain tumor group who had not undergone radiotherapy (Costello et al., 2004). Thanks to advances in radiation

administration techniques, it is possible to limit radiation exposure to normal cells and partially preserve cognitive functions.

The effect on cognitive function depends also on the type of radiation used. People who receive stereotactic radiosurgery and whole-brain radiation therapy for the treatment of metastatic brain tumors have more than twice the risk of developing learning and memory problems than those treated with stereotactic radiosurgery alone.

Phases of neuropsychological assessment



Chapter 3

Cognitive and neuroimaging correlates of brain tumors

At the beginning of the 20th century the discipline of clinical neuropsychology was born as a specific tool for precise quantification of cognitive impairment after brain damage, by using structured psychological tests. Since then the discipline was firmly established in the clinical evaluation of neurological disorders as a contribution to the description and localization of function in damaged brains. The subsequent development of increasingly sophisticated imaging measures allowed for a clear visualization of the brain. An innovative technological advance was the invention of functional exams like PET (positron emission tomography), SPECT (single photon emission computed tomography) and fMRI (functional magnetic resonance imaging). The signals obtained with PET and MRI are based on changes in blood flow, oxygen consumption and glucose utilization that very accurately relate to the cellular activity of the brain. The idea that local blood flow within the brain is intimately related to brain function led to a proliferation of new statistical methods of correlation between neuropsychological and imaging measures to better characterize the specific pathophysiological processes beneath functional and cognitive symptoms.

In the specific case of brain tumors, we discussed above the clinical value of neuroimaging technics in the diagnosis of this pathology. MRI gives some important information about the location and the size of the tumor mass, that are essential to planning and guide the neurosurgical resection. The simultaneous acquisition of behavioral and imaging measures allows a further step in the comprehension of the disease, because leads to a strictly correlation between the structural and functional changes of the brain and the changes in behavior. Modern theories of brain functions underline the importance of functional network in mediating cognitive functions. This

leads to a new consideration of brain-behavior relationship after focal lesion as a result not only of local structural damage but also as a more diffuse alteration of the networks that are functional connected to the lesion (Corbetta, 2010).

3.1 Cognitive and imaging correlation: an introduction

Lesion-symptom brain mapping

Brain–behavior relationships have frequently been approached with the assumption of unicity, which implies that one deficit corresponds to a single damaged area. On this basis, a traditional and widely used approach for linking neurological symptoms to specific brain regions involves investigating the presence of overlap in lesion location across patients with similar symptoms, procedure also known as lesion mapping. This approach is powerful and broadly applicable but has some important limitations. Firstly, it only determines the most frequent lesion, which may differ from the effective lesion. Secondly, similar symptoms may result from lesions in different locations, making localization to specific regions challenging. In fact, some mental functions, as in the memory domain, seem to be impaired in many focal injury locations, and most neurological deficits (e.g. motor weakness) can be caused by a lesion in various parts of a functional system (e.g. the pyramidal tract). Thirdly, the cognitive function subserved by the overlapping area may be only secondly impaired because of the interruption of tracts or association fibers by white matter damage, which may lead to disconnection with another area important for the same cognitive function. Thus, symptoms may result from lesion-induced functional alterations in anatomically intact, connected brain regions. Furthermore, the effect of multiple lesions may be cumulative, since the occurrence of some deficits requires the addition of several lesions (Boes et al., 2015).

The relevant limitations just described have led to a change in the traditional lesion mapping method, by orienting to new procedures of structural and functional imaging, that allow to include also the network effects.

Studying brain networks

For the first part of the history of cognitive neuroscience, the idea was that mental operations were localized to discrete brain regions. However, with the advent of modern neuroimaging tools such as PET and fMRI which allow to assess neuronal activity across the entire human brain, studies started to suggest that cognitive function is a distributed property represented by distributed networks across the brain. To trace axon pathways and therefore connectivity in the human brain, various methods have been used. Specifically, in vivo imaging methods include:

- diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI), which can reveal pathways starting from an arbitrary region of interest or from a region activated by a certain task; when seeding starts form a focal lesion, this method can be used to trace pathways damaged by the lesion;
- trans-cranial stimulation, in which focal magnetic or electric stimulation can reveal connections of stimulated areas in the form of distal activation sites;
- computational approaches, whereupon regional signals obtained during cognitive activations or during the resting state are subjected to complex statistical analyses to reveal inter-areal covariance that can be used to generate inferences concerning the connectivity of areas.
- Structural network nodes can be inferred from DTI or DSI patterns of convergence and divergence.

Structural networks. Neuroscientists soon realized that neural networks vary in magnitude: local networks are confined to single cytoarchitectonic fields or to immediately contiguous areas, while large-scale networks are composed of widely separated and interconnected local networks.

The neuroanatomical structure of large-scale brain networks provides a skeleton of connected brain areas that facilitates signaling along preferred pathways in the service of specific cognitive functions. The nodes of large-scale structural networks are areas in the brain defined by cytoarchitectonics, local circuit connectivity, output projection target commonality and input projection source commonality. A brain area can be described as a subnetwork of a large-scale network; this subnetwork consists of

excitatory and inhibitory neuronal populations (nodes) and connecting pathways (edges).

Functional networks. The connectivity patterns of structural networks determine the functional networks that can emerge. The topological form of functional networks (which nodes are connected to which other nodes) changes throughout an individual's lifespan and is uniquely shaped by maturational and learning processes. Large-scale functional networks exert coordinated effects on effector organs, subcortical brain structures and distributed cortical areas during a host of different cognitive functions, such as directing attention to specific stimuli. A functional network node can be detected as a focal brain region displaying elevated metabolism in PET recordings, elevated blood perfusion in fMRI recordings, or synchronized oscillatory activity in local field potential (LFP) recordings. Participation of a brain area in a large-scale functional network is commonly inferred from its activation or deactivation in relation to cognitive function. A group of brain areas jointly and uniquely activated or deactivated during cognitive function with respect to a baseline state can represent the nodes of a large-scale network for that function. The identification of functional network edges comes from different forms of functional connectivity analysis, which assesses functional interactions among network nodes.

Brain Connectivity. This represents a rapidly growing area of research. It is based on the investigation of functional and structural connections in the human brain, modeled as networks. Structural connections between brain region pairs are modeled from diffusion weighted imaging data, normally denominated as structural connectome or structural connectivity. Functional connections are modeled from functional magnetic resonance imaging data, by measuring temporal statistical dependences between brain region pairs, usually defined as functional connectivity or functional connectome. The analysis of brain networks has recently risen thanks to the development of new imaging acquisition methods as well as new tools from graph theory and dynamical systems. Examining human brain connectivity data offers new insights on how the integration and segregation of information in the brain relates to human behavior, and how this organization may be altered in neurological diseases and disorders. Disconnection

syndromes (Geschwind, 1965) are defined as higher function deficits that resulted from white matter lesions or lesions of the association cortices. More specifically, in this theory the sensory and motor cortex, together with the related inter-hemispheric connections, are connected with the "association" cortex, which functions as an obligatory relay station between sensory and motor regions. A lesion in the association cortex would produce a disconnection in the information processing flow. Three types of disconnection syndrome had been identified: sensory-limbic disconnection syndromes, sensory-motor disconnection syndromes, sensory-Wernicke's area disconnection syndromes. The interhemispheric disconnection plays also an important role in this approach, although it does not represent a separate callosal dysconnection syndrome. From a clinical perspective, these syndromes represent an alternative model by providing a useful framework for correlating lesion locations with clinical deficits (Catani and ffytche, 2005). The contemporary idea is that cognitive information is represented in highly interconnected and overlapping neuronal networks of the neocortex that transcend areas and modules by any anatomical definition: a complex, organized and dynamic system. The specificity of the networks derives essentially from the connections between elementary units (neuron assemblies) that are discontiguous and distributed throughout the cortex; thus, specificity derives not so much from the neuronal constituents of the network but from the relationships between them (Veldsman et al., 2019). According to more recent distributed dynamic models, the effect of a brain lesion may be better explained by considering a widespread network of functionally connected areas rather than on the basis of a single area. These associationist principles suggest that brain lesions should not cause highly specialized deficits, but rather clusters of deficits that reflect the imbalance of multiple interconnected anatomical networks (Thiebaut de Schotten and Foulon, 2017).

3.2 Measuring neuroplasticity in brain tumors

Neuro-imaging remains the most important instrument for diagnosis and monitoring brain tumors. The main advanced imaging technics developed so far are summarized below (Langen et al., 2017). All these imaging measures add clinical information to conventional MRI exam, useful for diagnosis of brain tumors:

- *Perfusion-weighted imaging (PWI)*: represents a measure of markers of tissue perfusion, such as relative cerebral blood volume (rCBV). This exam is a useful supplement of conventional MRI in some clinical cases, in particular for tumor grading and for differentiation between tumor progression and a pseudo-progression induced by the treatment.
- *Magnetic resonance spectroscopic imaging*: this exam allows a more accurate definition of tumor tissue, that can be particularly difficult in heterogeneous gliomas, by giving information on cell density, metabolic properties for differential diagnosis and genetic mutation.
- *Diffusion weighted imaging (DWI)*: represents a measure of water molecules motion within a single voxel and allows a more precise definition of tumor malignancy. Specifically, tumor tissue with high cell density shows a reduced water diffusivity.
- *FET-Pet*: currently, the amino acid PET is the most important application of PET in brain tumor.

Focusing on the specific case of brain tumors, a great contribution to the understanding of how cerebral neoplasms disrupt the brain's architecture and of brain's plasticity has been given by studies conducted on low grade gliomas (LGG, grade I-II WHO) by testing cognitive functions in patients and contemporarily mapping brain activation. Based on the observation that most patients with LGG present with seizures and have no neurological deficit, the assumption is that slow growing lesions induce progressive functional reshaping of brain networks. Duffau (2005) theorized four ways in which this could happen:

- function can persist within the tumor
- functional areas can be redistributed around the tumor
- function may be compensated by remote areas within the same hemisphere
- compensating networks can be recruited in the contralateral hemisphere

These observations suggest a hierarchical mechanism for plasticity, involving three levels recruited successively: first, an intrinsic reorganization within injured areas; second, the recruitment of other regions implicated in the original functional network in

the ipsilateral hemisphere but remote to the damaged area; and third, the solicitation of the homologous regions in the contralateral hemisphere (Heiss et al., 2003). These levels or reorganization have been demonstrated in a number of studies, respectively: magneto-encephalography studies have found that intra-tumoral activity is present in up to 36% of the patients; in central LGG, pre-operative neuroimaging techniques revealed that the hand representation was displaced and enlarged around the tumoral tissue (Desmurget et al., 2007); in gliomas within the motor system, activations of remote secondary motor areas in the same hemisphere as the lesion have been reported (Meyer et al., 2003); in LGG within the left inferior frontal cortex, translocations of Broca's area to the right hemisphere were observed (Holodny et al., 2002). Another common finding that demonstrates how plasticity plays a major role in preserving cognitive functions is that a fast-growing brain tumor causes more profound cognitive deficits than a slow-growing one.

Part 2: Research plan

Chapter 4

Research structure

4.1 General inclusion criteria

Patients admitted to the Clinical Neurology and to the Neurosurgery of Padua Hospital were recruited from July 2017 to April 2019.

- *Inclusion criteria*: patients with a clinical diagnosis of glioma (high or low grade) and meningioma.
- *Exclusion criteria*: metastases, recurrences, age under 18, history of neurological or psychiatric disorders, history of prior brain surgery, presence of other medical conditions that preclude active participation in research and/or may alter the interpretation of the behavioral/imaging studies, inability to maintain wakefulness in the course of testing and insufficient knowledge of the Italian language.

4.2 Time line

When possible, the same extensive neuropsychological assessment was performed at different time points (Fig. 4.1):

(T1) the week before surgery: this evaluation allowed detecting the impact of the tumor itself on cognitive functions.

(T2) the week after surgery: this neuropsychological evaluation quantified the variations in cognitive performance following neurosurgery.

(T3) one month after surgery, before the treatment (radiotherapy and chemotherapy): this assessment was compared to that performed at T2 to keep track of the cognitive profile over time.

(T4) four months after surgery, after the treatment: at the end of radiotherapy and chemotherapy the evaluation was performed to assess cognitive variations related to the treatment.

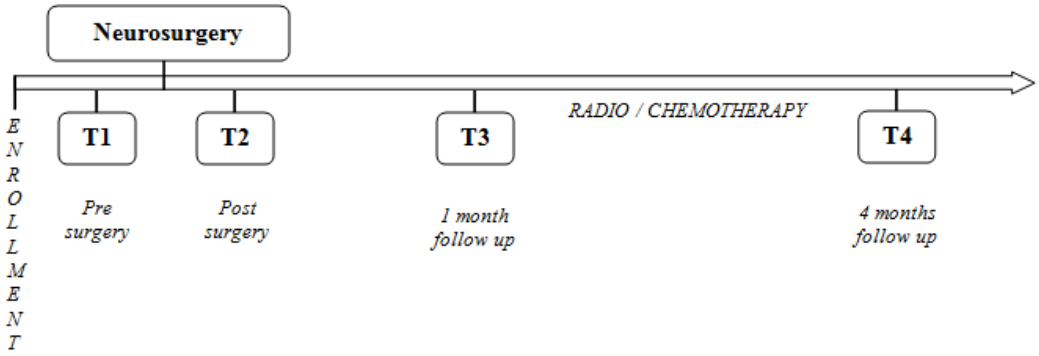


Fig. 4.1: timeline of the research procedure

4.3 Neuropsychological assessment

As argued above, there is no agreement about what tests are more sensitive in evaluating brain tumors. After considering the different indications from the literature, we developed a neuropsychological battery that was sensitive enough to detect cognitive impairment, but that was not so time-consuming to preclude repetition at different time points. The battery included tests that covered different cognitive domains (Fig. 4.2). Moreover the tests were well balanced between right hemisphere and left hemisphere functions: memory, attention, executive functions, language, visuo-spatial abilities, motor processing speed and manual dexterity. The evaluation required a general screening and structured tests sensitive to detect deficit in specific functions. The whole assessment lasted about an hour. The specific standardized tests composing the battery are described below.

The Oxford Cognitive Screen

As a general screening tool we selected the Oxford Cognitive Screen (OCS; Demeyere et al., 2015). Compared to other screening measures, such as the Mini Mental

State Examination or the Montreal Cognitive Assessment, the OCS measures both verbal and non-verbal (spatial) functions including also some such as apraxia and numerical abilities that are not measured by other screening tests (e.g. Mini Mental or Montreal Cognitive assessment). The OCS is relatively rapid which gives the opportunity to repeat testing at multiple time points. Secondly, we were able to compared the profile of tumor patients on the OCS with stroke patients tested as part of a different project (for a better discussion on this issue, see chapter 6).

OCS is a brief screening tool recently developed in the attempt to identify a gold standard for the acute cognitive screen of stroke patients. It is composed of language, visual attention, spatial neglect, praxis abilities, visual and verbal memory, calculation, number reading and executive function tasks (Table 4.1). The OCS can be administered in approximately 15 minutes and has shown high levels of inclusivity because of its aphasia and neglect friendly structure. It is freely available for assessment of Italian individuals and has been standardized on a large sample of healthy Italian participants stratified for age, gender and education level (Mancuso et al., 2016).

The OCS consists of ten sub-tests, administered in the following sequence:

- *Picture naming*: it assesses the level of expressive language. The patient is requested to name a sequence of four pictures.
- *Semantics*: the patient is asked to point a sequence of pictures, displaced in the page, on the base of their semantic category.
- *Orientation*: the participant is presented with some questions regarding the city in which she/he is, the time of the day, the month and the year. If she/he can't answer spontaneously, the same questions are presented in form of multiple choice.
- *Visual field*: this is a confrontation test to assess the patient's visual fields in case of hemianopia.
- *Sentence reading*: the patient is required to read aloud one centrally aligned 15-word long sentence. After the participant reads the sentence, the examiner reads the complete correct sentence to the patient, because the same sentence will be used later for the verbal memory task.
- *Number writing and calculation*: the first task is a number dictation, the second task requires four mental calculations (two additions and two subtractions). If the

participant cannot respond by free response, the same calculation are presented in form of multiple choice.

- *Broken hearts*: the patient is presented with a page containing 150 semi-randomly positioned full hearts and 50 broken hearts on the left and 50 on the right. The task is to cancel out only the complete hearts but not the broken hearts. Three different indices are calculated: total number of complete hearts canceled (measure of selective visual attention), egocentric neglect and allocentric neglect.
- *Imitation*: this test requires the patient to repeat exactly a series of meaningless hand actions made by the examiner
- *Recall and recognition*: the patient is asked to recall the previously read sentence (see above "sentence reading"). If the patient is unable to recall the sentence, a multiple choice task is presented. A further four multiple-choice questions are given to evaluate non-verbal memory through task recall. In this case the patient is required to point out which of 3 or 4 vertically aligned items had been previously encountered during the exam.
- *Trails task*: stimuli are pages with circles and squares of different sizes. The two baseline tasks require connecting with a line either circles or squares going down in size. The set shifting sub-test requires drawing a trail alternating between circles and squares, again going down in size.

Cognitive domain	**Sub-test**	**Cognitive function**
Language	Picture naming	Speech production, reading abilities, semantic knowledge, verbal comprehension
	Picture pointing	
	Sentence reading	
Memory	Orientation	Spatial and temporal orientation, verbal and visual memory
	Recall and recognition	
	Episodic memory	
Number processing	Number writing and calculation	Mental calculation, number comprehension and production
Attention-executive function	Broken hearts	Selective attention, visual search, spatial neglect, switching abilities
	Trails task	
Praxis	Imitating meaningless gestures test	Ideomotor apraxia

Table 4.1: Brief description of cognitive functions assessed by OCS subtests

Trail Making Test (TMT)

The TMT is a measure of selective attention and switching ability, speed, and mental flexibility. It requires the participant to connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in ascending order (part A) and 25 encircled numbers and letters in alternating order (part B). Scoring is expressed in terms of the time in seconds required for completion of each of the two parts of the test. Participants who do not complete part B within 7 min (420 sec) were assigned a time of 420.

Verbal Fluency Test

Tests of verbal fluency have been traditionally employed in clinical settings to measure executive dysfunctions. In particular, tests of verbal fluency are reported in literature as the most sensitive to detect the impairment of brain tumors patients. We used the Phonemic fluency version (Mondini et al., 2011) in which participants were asked to produce as many words as possible, excluding proper names, within one minute beginning with a given letter.

Digit Span

The Digit Span is a traditional task to assess verbal short-term memory: forward and reverse digit span were assessed to investigate selective verbal attention (Monaco et al., 2013). The participant is asked to repeat strings of digits increasing in length as said by the examiner in the same (forward) and in reverse (backward) order. The highest direct or reverse span achieved was used as the span measure.

Corsi Blocks tapping Test

This test represents a gold standard measure to detect visuo-spatial short term memory and implicit visual-spatial learning. The examiner displays 9 randomly positioned dice and with his/her hand points on a certain number of these dice. The participant is then asked to point at the dice in the same (forward) and in reverse (backward) order (Monaco et al., 2013).

Prose Memory Test

This test was administered in the immediate and delay recall forms (Mondini et al., 2011). It involves free recalls following auditory presentation of a short prose story and is considered to be a measure of verbal memory. Such prose stories are assumed to have greater ecological validity as compared to other memory measures. It consists in listening to a short prose passage and recalling its elements immediately and after 4 minutes.

Interference memory test (Mondini et al., 2011)

This test measures the degree of sensitivity of memory processes to interfering elements. A set of three letters is presented to the patient, who is asked to recall them after a counting interfering task with variable duration (10 seconds and 30 seconds).

Boston Naming Test (Kaplan et al.,1983)

The purpose of this test is to assess visual naming ability using 15 black and white drawings of common objects. Scores include the number of spontaneously produced correct responses and the number of cues requested in terms of semantic cueing and phonemic cueing, which are given if the patient is not able to give a correct response after semantic cueing. The total correct score is the sum of the number of spontaneously given correct responses.

Assessment of motor function

In order to collect data about the condition of the motor system we introduced two short tests:

- The Purdue Pegboard Test for manual dexterity and motor speed, evaluated for both right and left hand (Oxford Grice et al., 2003).
- The Motricity Index for muscular strength of upper and lower limbs.

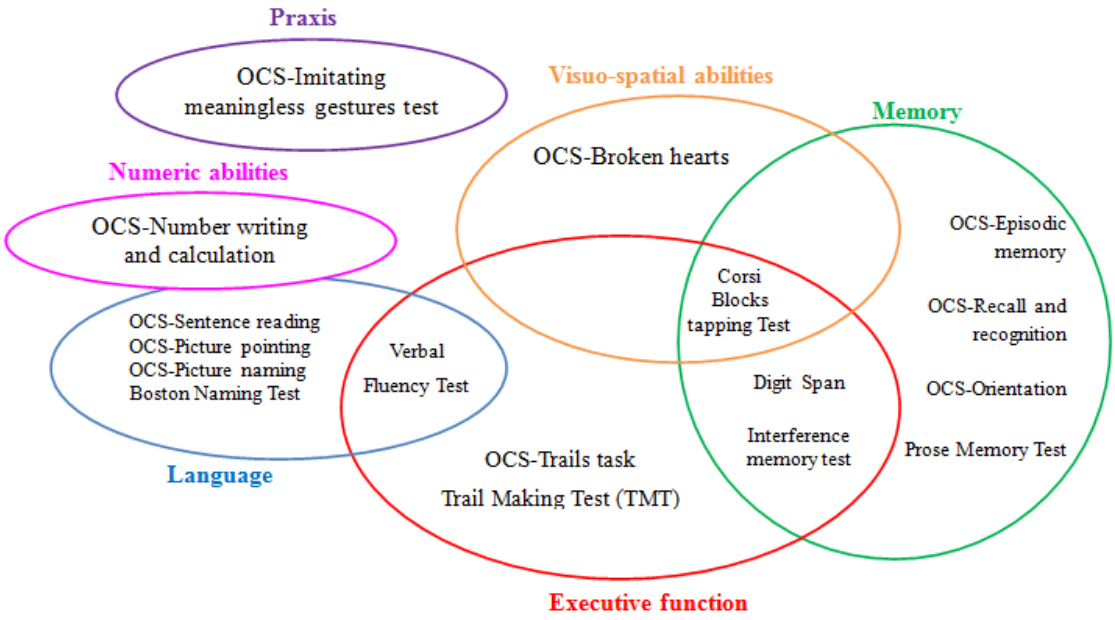


Fig. 4.2: Classification of cognitive domains evaluated with the neuropsychological battery

Affective and emotional evaluation

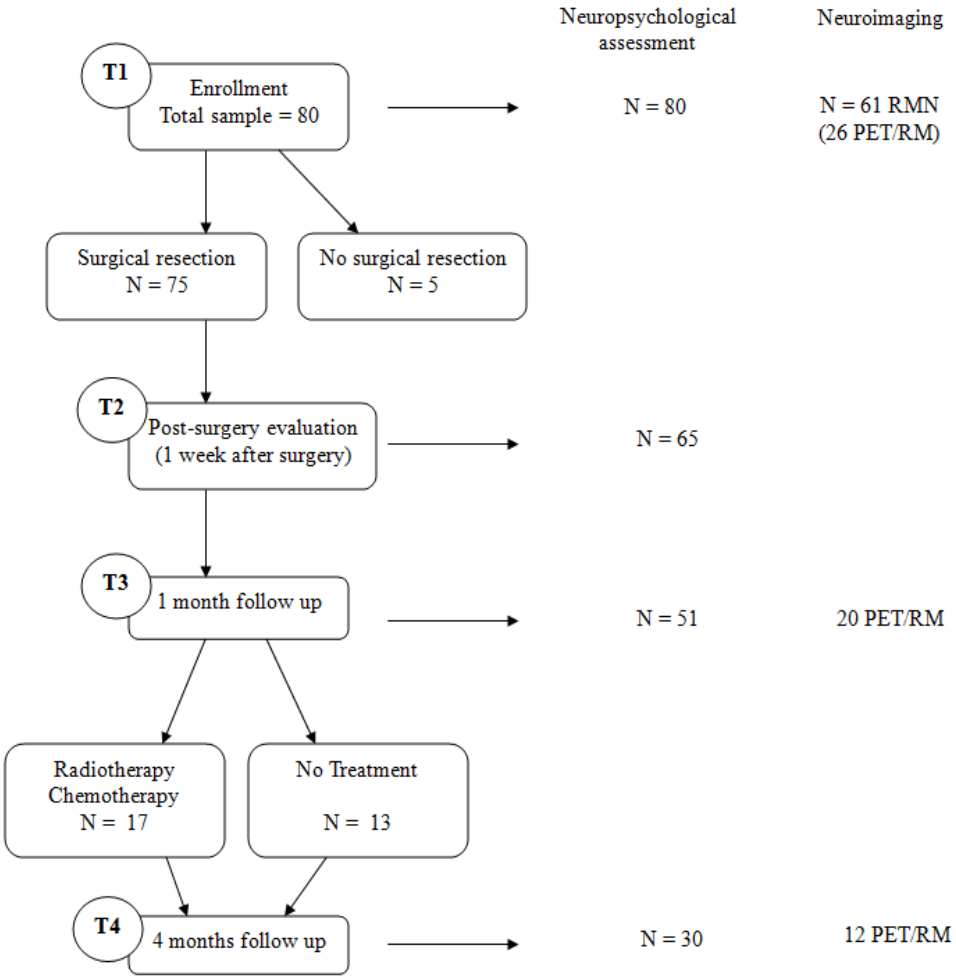
The emotional status and the health-related quality of life was also evaluated by two scales:

- Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), which is a brief scale made up of fourteen items that generates two different scores, one for depression and the other for anxiety.
- EORTC QLQ-C30 (Aaronson et al., 1993; Nolte et al., 2019), which is a specific instrument used in neuro-oncology to evaluate the impact of the disease on different everyday life areas. The scale is made up of 30 items distributed in five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and a quality-of-life scale, and single items that assess additional symptoms commonly reported by cancer patients (e.g., dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of disease and treatment.

4.4 Imaging data

For each partecipant, a pre-operative MRI scan was collected at the same time of the behavioral assessment for a voxel-wise structural analysis. Individual structural DICOM files were transformed into a NIFTI format (MatLab toolbox). Lesions were manually segmented on structural MRI scans (T1, T2, Flair) using the ITK-snap imaging software system111. Segmented lesions were mapped on the MNI152 atlas using the Clinical Toolbox for the SPM software system112. FSL software system was used to create (FslMerge) and display (FslEyes) the overlap of individual lesions on a standard brain atlas, thus producing an overlay map of the lesions.

Time points of the project



Part 3: Defining the cognitive profile of brain tumors

Chapter 5

Study 1
Descriptive analysis of cognitive effects of a cohort of brain tumor patients

5.1 Background

Identifying neuropsychological changes in brain tumors at an early stage of the disease may lead to a better therapeutic intervention to improve outcome. Imaging instruments, although diagnostic, do not give any information about the functional condition of the patient. To measure function it is thus necessary to conduct a neuropsychological examination.

It is well-known that brain tumors of different etiology have different impact on cognitive functions: aggressive high grade gliomas (HGG) are associated with reduced cognitive abilities (Bosma et al., 2007), low grade gliomas (LGG) do not lead to cognitive impairment for many years during the disease progression (Desmurget et al., 2007), while meningiomas cause some long-term cognitive consequences in processing speed and working memory efficiency (Meskal et al., 2016). The specific impact of each pathological type of tumor on brain tissue may explain the specific cognitive effect. For instance, pre-operative neuroimaging studies have shown that LGG lead to a neural reorganization that explains why these patients often appear normal to neurological exam (Duffau, 2005). In contrast, meningioma patients often suffer from presurgical cognitive deficits; however, since meningiomas do not directly damage the brain, this effect is likely due to a reduction of function due to perilesional edema or mass effect of the tumor. Some studies evaluated the relationship between meningioma location and cognitive performance. De Baene et al. (2019) examined how the location

of meningiomas impact cognitive performance. They measured neuropsychological data and MRI in 224 meningioma patients one day before surgery. For each cognitive domain, they tested whether the overlap with a specific brain region (out of 150 possible anatomical regions) was associated with worse performance. Overlap with both left middle and superior frontal gyrus were associated with worse complex attention scores. For the other domains, no association was found between tumor overlap with a region and cognitive performance. The authors concluded that patients with a meningioma in the left middle frontal gyrus were at potential risk for worse performance on cognitive flexibility and complex attention tasks, whereas patients with a meningioma in the left superior frontal gyrus were at potential risk for worse performance on complex attention.

These results suggest a possible link between the cognitive profile and the location of the lesion.

The dimensionality of deficit

An important issue in studying the cognitive effects of brain lesions concerns the concept of the dimensionality of deficits. The traditional modular view of the brain and teaching in Clinical Neurology predicts that lesions in different brain regions shall produce highly specific and different behavioral deficits. In fact, patients are usually enrolled in studies according to a specific behavioral syndrome (e.g. aphasia) with the aim of localizing the structural or functional basis of that impairment. However, most patients appear to have clinically a more "correlated" pattern of behavioral dysfunction, in which deficits in one domain, e.g. attention, are related with deficits in another domain, e.g. memory. Recent studies in stroke suggest that the variability of behavioral deficits in stroke across patients can be summarized by a few deficit components, each comprising multiple domain deficits (Corbetta et al., 2015). Accordingly, this low dimensionality of behavioral deficits is matched by a low dimensionality of structural and functional connectivity abnormalities (Siegel et al., 2016; Griffis et al., 2019). Overall these findings show that lesions in the brain cause more correlated than dissociated behavioral deficits, but this issue has never been addressed in tumors.

5.2 Aim of the study

Several studies so far have tried to define the cognitive profile of different types of brain tumor. To our knowledge, however, no studies has tried to understand what are the main component deficits across domains of function for different kinds of tumors. In other words what is the cognitive profile of cognitive deficits across many tumor patients? Are there specific deficits that are more sensitive to tumor damage?

Using the methodology developed by Corbetta et al. (2015), we investigated whether behavioral variability across subjects following brain tumors is better described by a large number of mostly independent syndromes or, instead, by a relatively small number of factors comprising components of correlated deficits within and between domains of function (language, attention, executive functions, memory). Moreover, we mapped the topography of tumor lesions in order to determine the association between lesion damage and the factor scores of behavioral impairment.

5.3 Materials and methods

Sample

Eighty patients with brain tumor from the Neurologic Clinic and the Neurosurgery Division were consecutively enrolled. Mean age was 60 years (range: 28-83) and the mean of education was 10.3 years (range: 2-18). The sample was equally distributed for gender (M=44; F=36). The histology was distributed as follows: gliomas (high grade=56, low grade=7) and meningiomas (n=17).

Neuropsychological assessment

Here we consider the pre-surgical cognitive evaluation. If the patient was scheduled for surgery resection the evaluation was administered in the week before surgery. For this analysis we considered the cognitive tests described previously (the Oxford Cognitive Screen, the Trail-Making-Test, forms A and B, Verbal fluency, Prose memory immediate and delay recall, Interference memory test, the Boston Naming Test, the forward and backward Digit span and the Corsi block-tapping test, the Nine hole

Purdue pegboard test). Specific cut-off values derived from the literature were used to evaluate the cognitive impairment in each test.

Statistical analysis

Dimensionality reduction was performed on the raw scores of the neuropsychological data using principal component analysis (PCA), which is a common data reduction strategy used to identify hidden variables or factors that could capture the possible correlation of behavioral scores across subjects (Turken and Dronkers, 2011). A high number of factors would be consistent with a large number of behavioral syndromes, while a small number of factors would be consistent with a few behavioral clusters common across many subjects. Subtests with more than 95% of null scores were excluded. Since components were expected to be correlated, an oblique rotation was used. R core Team 2018 program was used for all statistical analysis (For, 2018).

5.4 Results

Demographic characteristics of the sample

Although the general distribution of demographic characteristics was well-balanced in the whole sample, when we analyzed the specific distribution in the different sub-groups, selected by histology, some important differences emerged (Table 5.1).

The mean age of the high grade glioma cohort and meningioma cohort was similar, while the mean age of the low grade glioma was lower. Patients with low grade glioma were approximately 15 years younger than patients with other types of tumor.

Gender differences were also present between the groups, with more males with glioma and more females with meningioma. This different distribution reflects data on tumor incidence reported in literature (Sun et al., 2015).

The mean level of education was approximately the same in the different populations, with a lower value in the meningioma cohort.

	High grade gliomas N = 56	Low grade gliomas N = 7	Meningiomas N = 17
Age (mean)	**61**	**45**	**61.4**
18 - 30	1	0	0
31 - 50	13	4	2
51 - 70	25	3	11
> 70	17	0	4
Education (mean)	**10.5**	**12.2**	**8.9**
< 6	8	0	5
6 - 8	17	2	5
9 - 13	24	4	7
> 13	7	1	0
Gender			
Male	37	3	4
Female	19	4	13
Handedness			
Right	52	7	14
Left	3	0	1
Ambidextrous	1	0	2
Hemisphere			
Right	30	3	7
Left	26	4	10

Table 5.1: Demographic characteristics of the sample, divided by tumor etiology

Across-domains factor analysis

A Principal Components Analysis (PCA) was run on the neuropsychological data of the whole sample and, then, on the subgroup of glioma patients. The sample size of the subgroup of meningioma patients was not large enough to conduct PCA.

PCA on the total tumor cohort produced three main factors, which together accounted for 50% of the variance (Fig. 5.1). PC1 accounted for 31% of the variance and loaded on denomination, sentence reading, number writing, calculation and praxis; PC2 accounted for 11% of the variance and loaded on hearts overall accuracy, egocentric neglect, executive functions and Corsi forward and backward; PC3 accounted for 8% of the variance and loaded on memory (Table 5.2). Therefore, PC1

mainly loaded on left hemisphere functions like language, praxis, and calculation. PC2 mainly on right hemisphere functions like visuospatial attention, vigilance/performance, and spatial memory. Finally, PC3 loaded on verbal memory recall. It should be noted that the correlation of each PC with different scores is relatively low (0.2-0.4). This indicates that a significant amount of variance is not well captured by the PC structure identified.

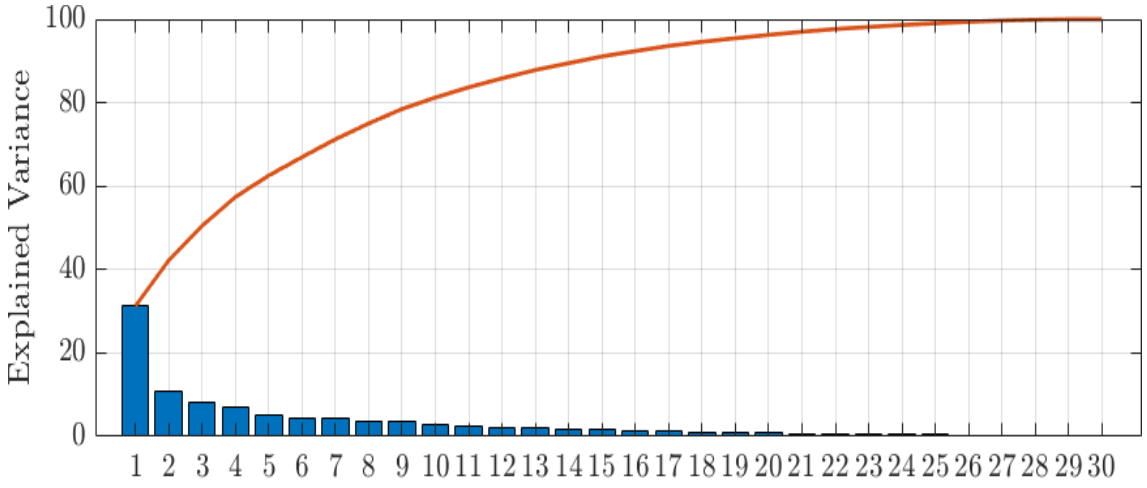


Fig. 5.1: Screening plot of explained variance in the whole sample. The principal components analysis run on neuropsychological data revealed 30 components in the performance of brain tumor patients. The first three components explained the 50% of the total variance. The red line represents the sum of the percentages of the variance explained by the components.

A separate analysis was run considering only data from glioma patients to rule out the possible influence of compression factors from meningiomas. The results replicated the components on the whole sample, suggesting that tumor type does not influence the correlation between behavioral deficits.

Test	PC 1	PC 2	PC 3
OCS-Denomination	-0.2		0.2
OCS-Visual Field-Right			0.2
OCS-Visual Field-Left			
OCS-Sentence reading	-0.4		
OCS-Number writing	-0.4		
OCS-Calculation	-0.3		
OCS-Hearths overall accuracy		0.3	
OCS-egocentric neglect-Right	-0.2	-0.2	
OCS-egocentric neglect-Left		-0.3	0.2
OCS-Imitating gesture-Right	-0.4		
OCS-Imitating gesture-Left	-0.4		
OCS-Verbal memory			0.3
OCS-Episodic memory			0.2
OCS-Executive function-simple		0.4	
OCS-Executive function-mixed		0.3	
OCS-Executive function-total	0.2	-0.2	
Memory Interference-10s			0.3
Memory Interference-30s			0.4
Prose Memory-Immediate			0.3
Prose Memory-Delay			0.4
TMT-A		-0.3	
TMT-B		-0.2	
Phonemic Fluency			0.2
Corsi test forward		0.3	
Corsi test backward		0.3	
Digit Span forward			0.2
Digit Span backward			0.2
Boston Naming Test			0.2
PEG-right hand	0.2		
PEG-left hand		-0.2	

Table 5.2: Loading on the first three PCs

Lesion Mapping

For each participant, a pre-operative gadolinium-enhanced T1- and T2-weighted and FLAIR MRI scan were collected. Nineteen scans were excluded, because of the reduced quality of the image. The final sample consisted in sixty-one scans, which were manually segmented using T1, T2 and Flair sequences. The segmentation was done by differentiating three type of lesions: tumoral tissue, edema and necrosis. Finally, two overlay maps of all lesions were obtained, the first by considering the tumor core only, that is tumoral tissue and necrosis (Fig 5.2), and the second by considering also the surrounding edema (fig 5.3).

The lesion predominantly involved frontal and temporal cortex, especially in the right hemisphere. The degree of overlap was relatively low (~20% max). When the edema was considered most of the overlap was in the frontal, parietal, and temporal white matter.

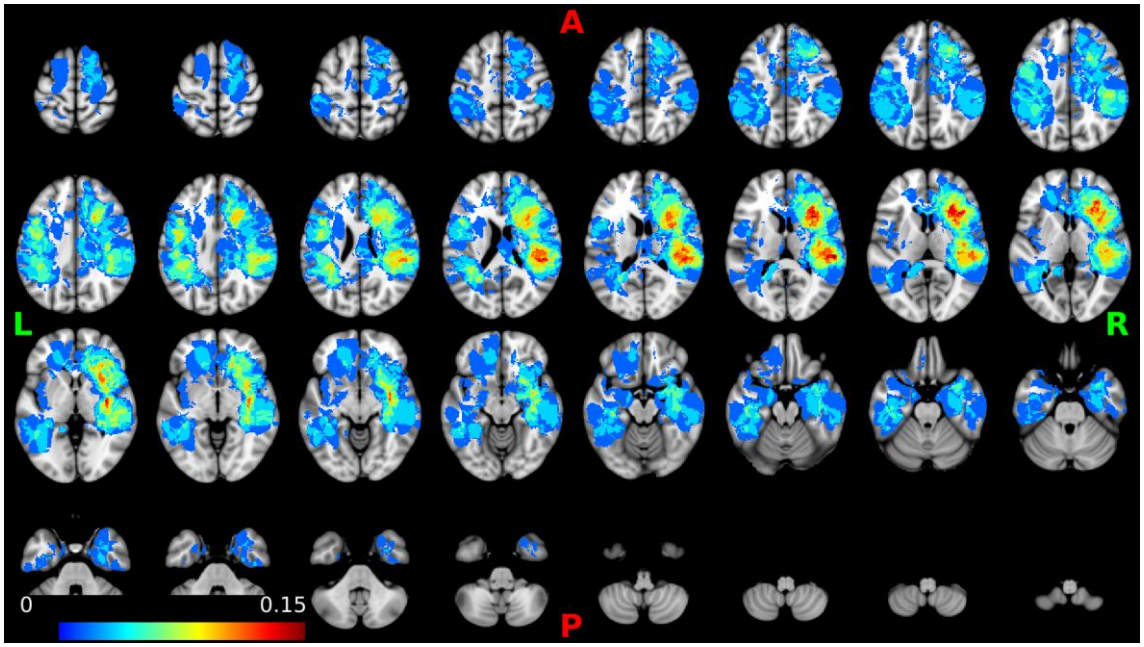


Fig. 5.2: Tumor lesion frequency map, by considering the tumor core (tumoral tissue and necrosis). The red color indicates higher overlap between lesions.

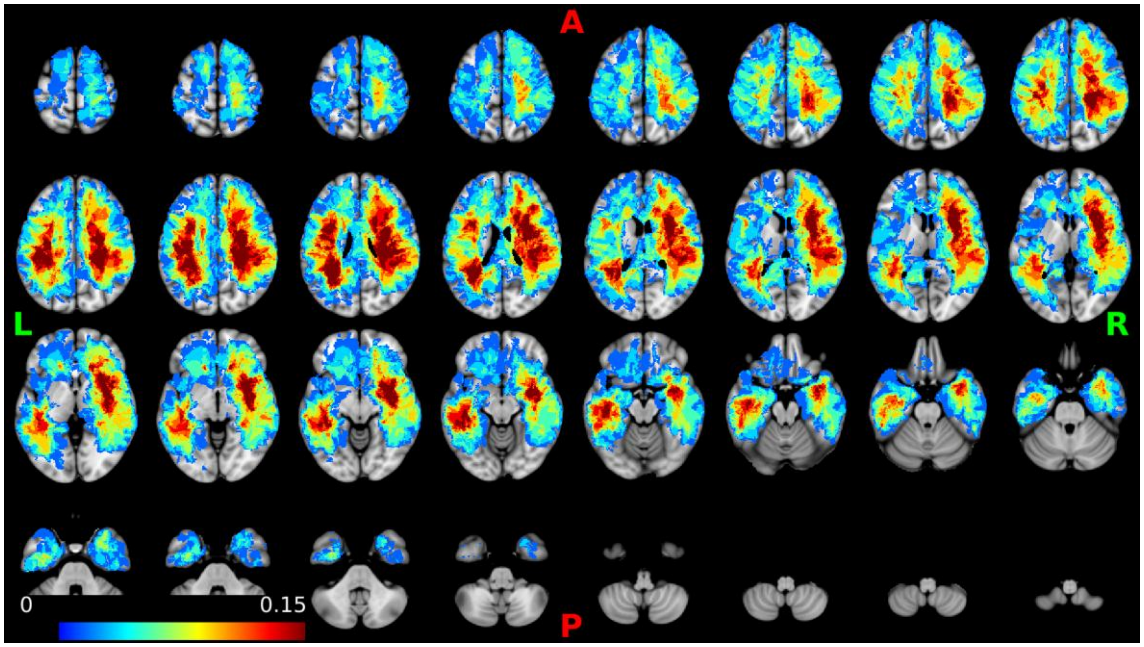


Fig. 5.3: Tumor lesion frequency map, by considering the tumor core and the surrounding edema. The red color indicates higher overlap between lesions.

5.5 Discussion

It is already well-known that cognitive disease represents a significant problem in brain tumors, because of its impact the everyday life of the patient. The characterization of the cognitive profile of our sample identified three main factors that explained about half of the variance. Factor 1 loaded more on language and praxis dysfunction, factor 2 loaded more on attention and visuo-spatial dysfunctions, factor 3 loaded on memory dysfunction. This small number of factors in the characterization of the cognitive impairment following a brain tumor suggests that focal damage can impair cognitive functions at a global level. This nature of cognitive dysfunction can be explained by both the direct and indirect impact of the tumor on functional connectivity. It has been already demonstrated that a reduction of functional connectivity in the language network occurs after left hemispheric brain gliomas. The tumor may influence connectivity in two different directions: on one side it reduces the connectivity in the ipsilesional hemisphere, based on the tumor location, on the other side, it also causes a reduction of inter-hemispheric connectivity, with a consequence on areas that are distant

from the specific site of lesion (Briganti et al., 2012). However, it should be also noted that the loading of each test score with each principal component was relatively low (±0.2-0.3). This could be related to the relatively small number of patients, or it could mean that there is more individual variability at the individual level than captured with this analysis.

The conclusions of this descriptive analysis led to a second question: is this neuropsychological battery sensitive to pick up subtle cognitive deficits before and after surgery?

Chapter 6

Study 2
Comparing cognitive profile of brain tumor with the cognitive profile of a different neurological lesion (stroke)

We have widely discussed that brain tumors have different behavioral consequences, not only from a neurological point of view, but also in term of cognitive damage. However, the particular profile of cognitive dysfunction may be related to the specific impact of tumors on brain function. The gradual displacing of brain structure without neural destruction for a long period, indeed, may recruit mechanisms of neural plasticity that might lead to a reorganization of cognitive functions. Therefore, it is not clear whether the cognitive profile of brain tumor patients may be different as compared to that of a neurological disorder like stroke that is also "focal", but that affects neurological function suddenly through mechanisms of ischemia and neuronal death.

Several studies have been conducted to characterize the consequences of brain tumors on cognitive functions. These studies have suggested the importance of an extensive neuropsychological protocol in the pre and post-operative stages (Papagno et al., 2012; Dallabona et al., 2017; Ali et al., 2018). However, no study so far has defined the cognitive profile of brain tumors taking into account the specific neurological nature of this pathology, and compared it with another neurological disorder involving a different pathophysiological process. Stroke represents an excellent term of comparison precisely because of its specific nature. Indeed, from a pathophysiological point of view, brain tumors and stroke affect the cerebral tissue in different ways: the dysfunction caused by stroke depends on the direct and radical destruction of neurons.

The aim of this study was to compare the neuropsychological profiles of a group of patients with brain tumor with a group of patients with focal stroke, in order to define the specific impact of different etiologies on cognitive status and to better characterize the cognitive profile of brain tumors.

6.1 Background

Pathophysiology of stroke: a brief introduction

Stroke is a medical condition in which poor blood flow to the brain results in cell death. According to its pathological background, stroke can have an ischemic or hemorrhagic origin. Lesion focality is a central feature of stroke. Constant blood flow can be interrupted in a specific vessel causing focal brain damage. Cell death is caused by hypoxia and subsequent ischemia of the cerebral tissue in the corresponding vascular territory. During ischemic stroke a spectrum of severity is generally observed in the affected region of the brain. Part of the brain parenchyma (core) undergoes immediate death, while others may only be partially injured with potential to recover (penumbra). In the case of hemorrhagic stroke, hypoxia resulting from a blood vessel rupture in the brain, is responsible for subsequent focal damage. Stroke clinical manifestations are characterized by an acute, typically focal, onset of neurological deficits. Clinical presentation has been traditionally differentiated according to vessels affected and subsequent vascular territories involved. Many distinct neurovascular syndromes (including broad neurovascular syndromes and function specific syndromes) would arise from damage to functionally specialized cortical and subcortical centers. They have been described as follow:

- *Internal carotid artery (ICA)*: a massive infarction may occur involving the anterior two thirds of the corresponding hemisphere. This results in a severe contralateral hemihypoesthesia and hemiplegia or hemiparesis, and lateral homonymous hemianopsia. In the dominant hemisphere there can also be aphasia, while in the non-dominant hemisphere apraxia or anosognosia.
- *Middle cerebral artery (MCA)*: an obstruction at its origin causes a vast infarction in frontal, parietal and temporal areas and therefore a similar clinical

presentation as in ICA syndrome. If, however, the obstruction happens in one of the MCA's branches there will be only partial syndromes: in case of superior branch obstruction the symptoms will be a mainly facial-brachial contralateral motor and sensitive impairment, eventually associated with global or mainly motor aphasia; an inferior branch obstruction will cause contralateral homonymous hemianopsia, a Wernicke's aphasia in left lesions or hemineglect in right lesions.

- *Anterior cerebral artery (ACA)*: clinical presentation usually consists in contralateral lower limb motor and sensitive deficits, motor transcortical aphasia and behavioural impairment (apathy and abulia).
- *Vertebral artery (VA)*: this vessel branches to the medulla and usually branches in the posterior inferior cerebellar artery (PICA). A specific presentation of an obstruction of the VA is Wallenberg's syndrome, also known as lateral medullary syndrome, which consists in: vertigo, nystagmus, dysarthria, dysphagia; homolateral hemihypoesthesia of the face, Bernard-Horner syndrome, hemiataxia; contralateral thermo-dolorific hemihypoesthesia of the body
- *Basilar artery (BA)*: a complete obstruction of this artery causes tetraparesis and abnormalities of cranial nerves with very high morbidity and mortality. A more distal obstruction of the BA can cause multiple infarctions in the thalamus, mesencephalon and temporo-occipital lobes.
- *Posterior cerebral artery (PCA)*: depending on which deep branches are involved, patients may present contralateral hemisoma anesthesia with mild hemiparesis (thalamus infarction), homolateral oculomotor paralysis with contralateral hemiparesis and/or ataxia (mesencephalon), hemiballismus or hemichorea (subthalamic nucleus). If on the other hand the obstruction involves the cortical branches of the PCA, the main symptom consists of contralateral homonymous lateral hemianopsia; an infarction in the dominant hemisphere could also cause alexia, anomia and visual agnosia. Bilateral occipital lobe infarction presents with cortical blindness, i.e., bilateral homonymous hemianopsia.

From a clinical and prognostic perspective, acute severity after stroke is most frequently assessed through the National Institutes of Health Stroke Scale (NIHSS).

Cognitive profile: Cognitive deficits occur in 50–78% of stroke patients with deficits in different cognitive domains, depending on the vascular territory involved: language, spatial attention, memory, praxis, executive functions and speed of information processing (Nys et al., 2007; Jaillard et al., 2009; Gottesman and Hillis, 2010). Since emboli are more likely to migrate to the grey–white matter junctions or to the inferior division of the middle cerebral artery territory, the most common cognitive deficits after stroke are problems with language (aphasia) or with spatial processing (neglect). The type of language deficit (comprehension, production, speech articulation, reading, spelling, or naming) or type of hemispatial neglect (one half of objects or one half of space) depends on the location of ischemia. Other deficits that result directly from a stroke or from adjacent areas of hypoperfusion regard working memory, attention, learning, calculation, visual perception, or executive functions. Cognitive assessment in the sub-acute phase significantly predicts cognitive impairment at 3–6 months after stroke (Dong et al., 2012). It has been found that the 40% of patients with cognitive impairment in acute stage still demonstrate the same impairment at a 2-year follow-up (Rasquin et al., 2004; Turunen et al., 2017).

Stroke is thought to cause cortical damage and highly specific behavioral syndromes in line with a modular view of brain organization and functions. Specific behavioral symptoms would reflect the functional specialization of different brain modules, while syndromic correlations would result from coupled damage to cortical regions specialized for different domains. A left middle cerebral artery stroke causes a Broca's aphasia and right hemiparesis for concurrent damage to the left inferior frontal cortex and precentral cortex, while a lesion to the inferior temporal cortex, known as the fusiform gyrus, selectively causes prosopagnosia, the inability to recognize faces. However, recent studies have shown that behavioral deficits post-stroke are more correlated than previously believed, and that symptoms that are putatively related to different regions of the brain even at distance or even in opposite hemispheres may be correlated. Corbetta et al. (2015) demonstrate that in a prospective sample of 132 stroke patients, the majority of variability in behavioral performance was explained by three

factors. They investigated impairments in 5 main domains (motor, attention, language, visual memory and spatial memory), and found that most of the variance in each of these domains were explained by a single factor. In other words, patients with problems speaking also had deficits of reading and auditory comprehension. Furthermore, two thirds of partecipants had deficits in more than one domain. Finally, when analysing across domains, it was evident that about 70% of the variability could be explained by three components. Another important finding was that this correlation between behavioral impairments was also present at 3 and 12 months after the event, indicating that these behavioral patterns represented robust phenotypes of impairment at the population level (Ramsey et al., 2017). The stability of behavioral clusters, their ability to account for variance over time and the pattern of moderation on recovery suggest that, at the population level, stroke lesions commonly cause a low dimensional set of behavioral deficits and clusters of deficits, which seemingly reflect a correlation of physiological processes that are represented in a distributed network rather than in local modules (Corbetta et al., 2018).

Comparing stroke and brain tumors

Traditionally research in neuropsychology has focused on the behavioral effects of focal brain disorders, e.g. tumors or stroke. Patients with brain tumors and stroke are the most frequent patients enrolled in research based on lesion method in order to investigate the behavioral consequences of brain lesions. Typically these patients with different etiology are grouped together. However it is unknown if tumor and stroke affect the same cognitive function even when the structural lesion affects the similar location in the brain. From a pathophysiological point of view, brain tumors and stroke affect the cerebral tissue in different ways. Stroke causes an acute disruption of local neuronal activity. Tumors in contrast grow slowly and determine a displacing of neural structure without a neural destruction for a long period, so they may affect function through different mechanisms (e.g. edema, or mechanical pressure) which may in theory induce an adaptation, hence a potentially different pattern of deficits. Because of these physiological differences, stroke and brain tumor may recruit mechanisms of neural plasticity in different ways. Only few studies have directly compared the behavioral and

cognitive deficits induced by these two kinds of focal lesions. Anderson et al. (1990) compared the neuropsychological profile of patients with stroke and brain tumors matched for site of lesion. In this study, 17 subjects with a focal cerebral neoplasm were individually matched to subjects with a single focal stroke in the same area: the aim was to evaluate if tissue damage induced by either stroke or tumor in the same position gave similar or different neuropsychological deficits. Tumor lesions were matched with strokes of equal or smaller volume given the latter may cause more severe deficits; patients with stroke were tested at least 4 weeks after the event, thus after some form of possible recovery, while patients with tumors were tested before any form of treatment. This research produced the following results: (i) behavioral deficits were weaker in patients with tumor than in patients with stroke; (ii) deficits were more variable in tumors, and less specific for the site of damage than in stroke; (iii) very extensive tumors may cause no cognitive impairment. The authors concluded that these results are in line with the pathophysiology of the two different types of brain lesion. A tumor infiltrates or displaces the brain tissue without destroying the neurons for a long time. For this reason, the cerebral tissue has time to reorganize and restore its function. On the opposite side, a stroke causes an immediate disruption of neurons. Cipolotti et al. (2015) also compared the impact on neuropsychological performance of four different etiologies: strokes, high grade tumors, low grade tumors and meningiomas and found no significant difference in the cognitive performance. This study, however, considered only lesions confined to the frontal lobe and tested performance only on executive tasks. Furthermore, tumor patients were enrolled at the post-operative stage, after the surgical resection.

From a pathophysiological point of view, only few studies have directly compared the recovery process in stroke and brain tumors. Functional recovery is considerably better in the context of slow-growing injuries than after acute lesions, because slow and acute lesions involve very different patterns of reorganization (Heiss et al., 2003; Desmurget et al., 2007). This disparity is probably due to the greater neural re-mapping allowed by a slow-growing lesion (such as brain tumor), compared to an acute lesion (stroke). More specifically, in case of stroke the recovery involve mainly ipsilesional structures, whereas in case of brain tumors plasticity involves both adjacent and distant areas, in the ipsilesional and contralesional hemispheres. Likewise, an acute

lesion such as a stroke, shows much greater cognitive dysfunction when compared to patients with chronic lesions of the same size, even during recovery when some form of compensation has occurred (Maesawa et al., 2015). Brain plasticity seems to follow a hierarchical model both in brain tumor and in stroke, however brain tumor recovery adds two specific processes: firstly, compensations can involve areas that are not part of the functional network; secondly remote compensations in the intact or lesioned hemisphere are not a marker of pure recovery (Desmurget et al., 2007). The clinical implications of these observations are significant, because, while acute injuries as stroke cause irrevocable functional impairment, a slow-growing lesion may allow a complete recovery of function.

6.2 Aim of the study

The concept of low dimensionality of deficits has been explained in previous sections. Behavioral studies often concentrate only on specific deficits like aphasia or prosopagnosia with the assumption that injury to the brain causes many behavioral syndromes, but recently it was demonstrated that stroke causes only a few clusters of correlated deficits, a low-dimensional set of cognitive impairment (Corbetta et al., 2015).

We wondered whether the pattern of correlation found in stroke could be replicated in tumors. Moreover, even though clinically tumors tend to produce less severe deficits than strokes, would the pattern of correlation be the same or different? Therefore, the aim of this study was to compare, using the same neuropsychological battery, behavioral deficits in stroke and tumor patients, and to investigate whether the same pattern of deficit correlations emerged in both conditions. Such a result would be significant from a clinical point of view to track in a simple way cognitive outcome during treatment.

6.3 Materials and Methods

Sample

Patients admitted to the Clinical Neurology and to the Neurosurgery Unit of Padua Hospital were recruited from December 2017 to April 2019.

Eighty patients with brain tumors and 133 patients with first symptomatic ischemic or hemorrhagic stroke were initially included. For all patients these exclusion criteria were considered: age under 18, history of neurological or psychiatric disorders, previous central nervous system surgeries, presence of other medical conditions that precluded active participation in research and/or might alter the interpretation of the behavioral/imaging studies, inability to maintain wakefulness in the course of testing, and insufficient knowledge of the Italian language. In case of brain tumors, metastases and recurrences were also considered as exclusion criteria. Stroke patients were considered only in case of up to two clinically silent lacunes, less than 15 mm in size on CT scan; multifocal strokes (i.e., more than one vascular territory) were excluded. Since performance on the cognitive tests requires a certain degree of intellectual ability and compliance, the stroke patients considered in this study were mild in severity (evaluated using the NIHSS). In order to have a cohort of patients with a complete neuropsychological battery, we did a further selection on the stroke sample, by considering for the analysis only the patients who concluded the whole battery. This procedure makes stroke and tumor samples more comparable from a cognitive point of view. Indeed, as a rule patients with tumors have milder cognitive deficits and no major sensory motor deficits or aphasia, therefore a comparison with mild stroke cases is appropriate. The final stroke sample consisted in 77 patients.

Tumor patients were evaluated before surgical or pharmacological treatment, stroke patients were evaluated within two weeks after the event. The tumor cohort consisted in 17 meningiomas and 63 gliomas, of which 7 low grade and 56 high grade. The stroke cohort consisted in 14 hemorrhagic and 119 ischemic.

Neuropsychological and clinical assessment

The neuropsychological assessment has been described previously and consisted in a screening battery (OCS) and structured tests specific for cognitive function. The OCS was used with the aim of defining a specific cognitive assessment for stroke population, that allows measuring some functions (verbal memory or executive functions) that are often hard to evaluate because of the high severity of language disease (Pasi et al., 2013). For this reason, OCS represents the most suitable tool for the comparison between stroke and brain tumors.

Clinical evaluation for stroke patients was done through the National Institutes of Health Stroke Scale (NIHSS), as a measure of the severity of the disease. The NIHSS is composed of 11 items each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed and a total score of impairment is obtained (range 0-42, in which the maximum represents the highest grade of impairment).

Subjects in the stroke cohort were tested within two weeks from their event; subjects in the tumor cohort were tested before any kind of medical or surgical treatment, during hospitalization for imminent neurosurgery procedure or for a first clinical manifestation.

Imaging

For each participant, a CT or MRI scan was collected for a voxel-wise structural analysis at the same time of the behavioral assessment. Individual structural DICOM files were transformed into a NIFTI format (MatLab toolbox). Lesions were manually segmented on structural MRI and CT scans using the ITK-snap imaging software system111. Segmented lesions were mapped on the MNI152 atlas using the Clinical Toolbox for the SPM software system112. FSL software system was used to create (FslMerge) and display (FslEyes) the overlap of individual lesions on a standard brain atlas, thus producing an overlay map of all lesions.

Statistical analysis

Firstly, dimensionality reduction was performed on the performance data using principal component analysis (PCA).

As second step, a logistic regression model was run to test the discriminating power of neuropsychological tests in differentiating the two cognitive profiles. The aim of the model is to establish the probability by which an observation can generate one or the other factor; it can also be used to distinguish observations into two categories (Stock and Watson, 2015). The result of the analysis is the odds ratio (OR), which is a measure that defines the likelihood that an event will occur, expressed as a proportion of the likelihood that the event will not occur. Therefore, if A is the probability of subjects affected and B is probability of subjects not affected, then odds = A/B. An odds ratio of 1.5 indicates that event A, e.g. stroke, is 1.5 more likely than event B, e.g. tumor. In the model these demographic variables were controlled: age, gender, education.

6.4 Results

Demographic characteristics of the sample

Of the 133 stroke patients enrolled, only 77 were able to perform each task. To verify if this selection led to a bias in severity, the NIHSS score of the final sample (mean=2.86; DS=3.35) was compared with the NIHSS of the total sample (mean=2.06; DS=2.02). There was no significant difference in the mean score of the NIHSS between the whole group and the subset with all tests (p=0.06), so we can conclude that the final stroke cohort does not represent only less severe cases.

The demographic characteristics of the two cohort of patients (brain tumor and stroke) are described below (Table 6.1). The two groups were similar in term of mean age and mean of education. Gender differences were similar between the two cohorts, with an overall majority of males affected and only a slightly higher percentage of males in strokes. Handedness was also similar in the two cohorts with a slightly higher percentage in tumor patients.

	Brain tumor N = 80	Stroke N = 77
Age (mean)	60	65
Education (mean)	10.3	11.6
Gender (M/F)	44/36	51/26
Handedness (R/L)	76/4	68/9

Table 6.1: Demographic characteristics of the two sample (brain tumors and stroke)

Across-domain factor analysis

The PCA was run on neuropsychological data of the whole sample and on the two different sub-groups (stroke and brain tumors) separately.

The Principal Component Analysis on the tumor cohort produced three main factors, as described above, which together accounted for 55% of the variance (Fig. 6.1). PC1 accounted for 34% of the variance and loaded on denomination, verbal memory, episodic memory, memory with interference, prose memory, phonemic fluency, Boston naming test; PC2 accounted for 13% of the variance and loaded on hearts overall accuracy, egocentric neglect, executive functions, TMT A and B, Corsi forward and backward; PC3 accounted for 8% of the variance and loaded on sentence reading, calculation, executive functions and egocentric neglect (Table 6.2).

PCA on the stroke cohort also produced three main factors, which together accounted for 50% of the variance (Fig. 6.1). PC1 accounted for 33% of the variance and loaded on denomination, verbal memory, memory with interference, prose memory and Boston naming test; PC2 accounted for 10% of the variance and loaded on hearts overall accuracy, executive functions, TMT A and B, Corsi and Digit Span backward; PC3 accounted for 7% of the variance and loaded on egocentric and allocentric neglect and executive functions (Table 6.2).

In conclusion analysis across domains produced three main factors that accounted for majority of the variance, both in tumor and stroke. Factor 1 consisted in language and memory impairments; factor 2 consisted in attention, executive functions

and visuospatial impairments. Factor 3 was different in the two groups: biased toward language and executive function in brain tumors, and toward visuospatial functions and memory in stroke.

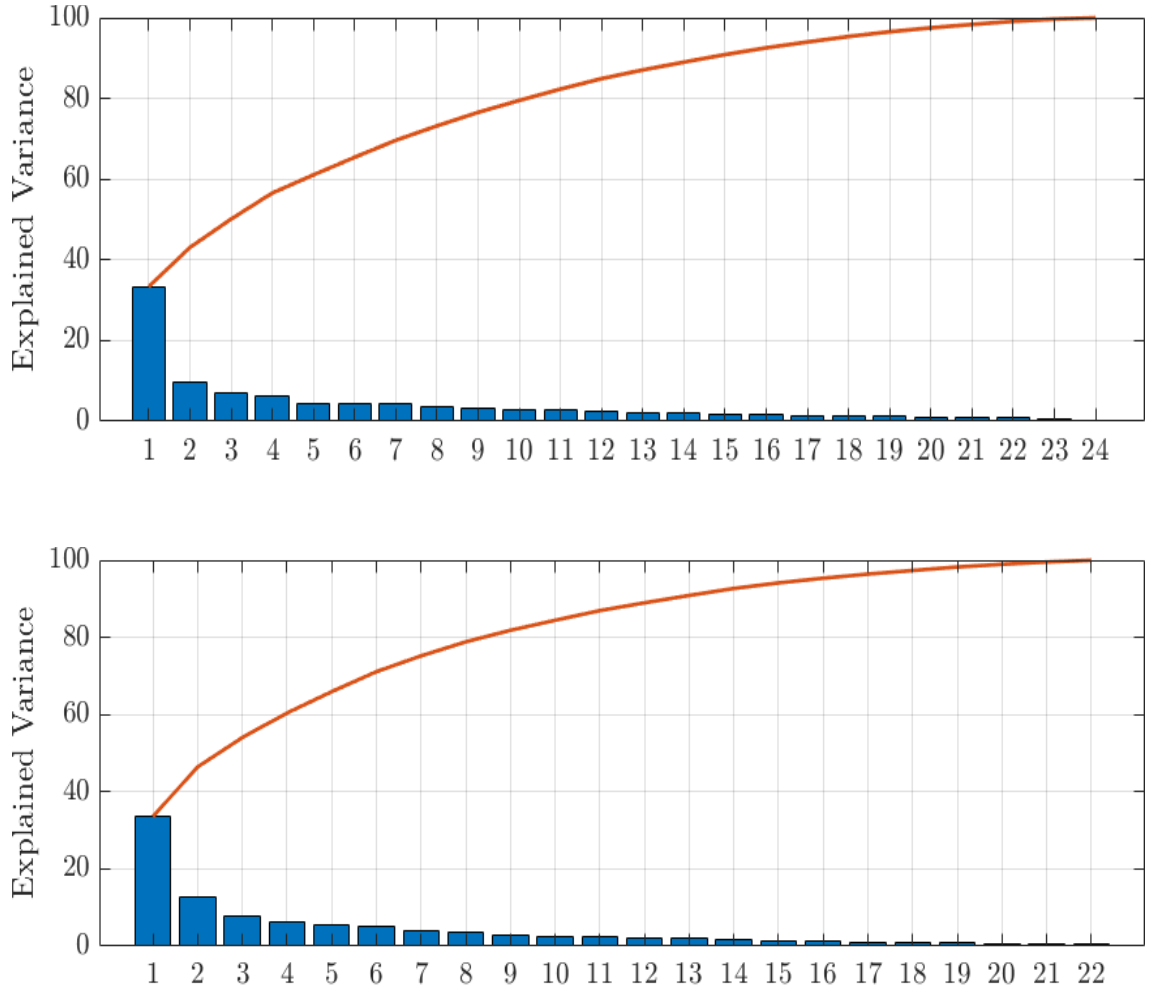


Fig. 6.1: Screening plot of explained variance in the two sample. The principal components analysis run on neuropsychological data revealed 24 components in the performance of stroke patients (above) and 22 in the performance of brain tumor patients (below). In both samples, the first three components explained the 50% of the total variance. The red line represents the sum of the percentages of the variance explained by the components.

	Brain tumors			Stroke		
Test	**PC 1**	**PC 2**	**PC 3**	**PC 1**	**PC 2**	**PC 3**
OCS-Denomination	**0.2**		**0.2**	**0.3**		
OCS-Sentence reading			**0.5**	**0.2**		**0.2**
OCS-Number writing						
OCS-Calculation			**0.4**	**0.2**		
OCS-Hearths overall accuracy		**0.3**	**0.3**	**-0.3**	**0.5**	
OCS-egocentric neglect-Right	**0.2**		**0.4**		**0.2**	**-0.5**
OCS-egocentric neglect-Left	**-0.3**	**0.4**			**0.2**	**0.5**
OCS-allocentric neglect-Right						**-0.4**
OCS-allocentric neglect-Left						**0.3**
OCS-Verbal memory	**0.3**		**0.2**	**0.3**		**0.2**
OCS-Episodic memory	**0.2**		**0.2**	**0.2**		**0.2**
OCS-Executive function-simple		**0.4**			**0.3**	**0.4**
OCS-Executive function-mixed		**0.3**	**0.3**		**0.2**	
OCS-Executive function-total						
Memory Interference -10s	**0.3**			**0.3**		
Memory Interference - 30s	**0.3**			**0.2**		
Prose Memory-Imediate	**0.3**			**0.4**		
Prose Memory-Delaied	**0.3**			**0.4**		
TMT-A		**0.3**			**0.4**	
TMT-B	**0.2**	**0.2**			**0.3**	
Phonemic Fluency	**0.2**	**0.4**		**0.2**		
Corsi test forward		**0.4**				
Corsi test backward					**0.4**	
Digit Span forward	**0.2**			**0.3**		
Digit Span backward	**0.2**				**0.4**	**0.2**
Boston Naming Test	**0.3**			**0.4**		

Table 6.2: Loading on the first three PCs of the two groups of patients (brain tumors and stroke).

Logistic regression

We plotted the frequency distribution of the test scores performed by the two groups. As shown in the figure 6.2, stroke and tumors seemed to fail in different tests: brain tumors obtained lower scores in memory and executive tests more frequently (i.e., interference memory, prose memory, digit span backward, phonemic fluency), while stroke patients seemed to have a worse performance in language and attentional tasks (i.e., OCS Denomination, Boston Naming Test, TMT A and B). The differences in the cognitive profile of stroke and tumor patients were then investigated by means of a logistic regression with age, education gender, lesion side (right vs. left), and tests scores as predictors. Performance in four tests significantly discriminated a patient with a tumor or stroke. High scores in denomination (z=-2.6; p=0.008) and calculation (z=-2.8; p=0.003) were more probable in patients with tumor, while high scores in episodic memory (z=2.8; p=0.005) and phonemic fluency (z=2.1; p=0.03) were more probable in patients with stroke (fig 6.3).

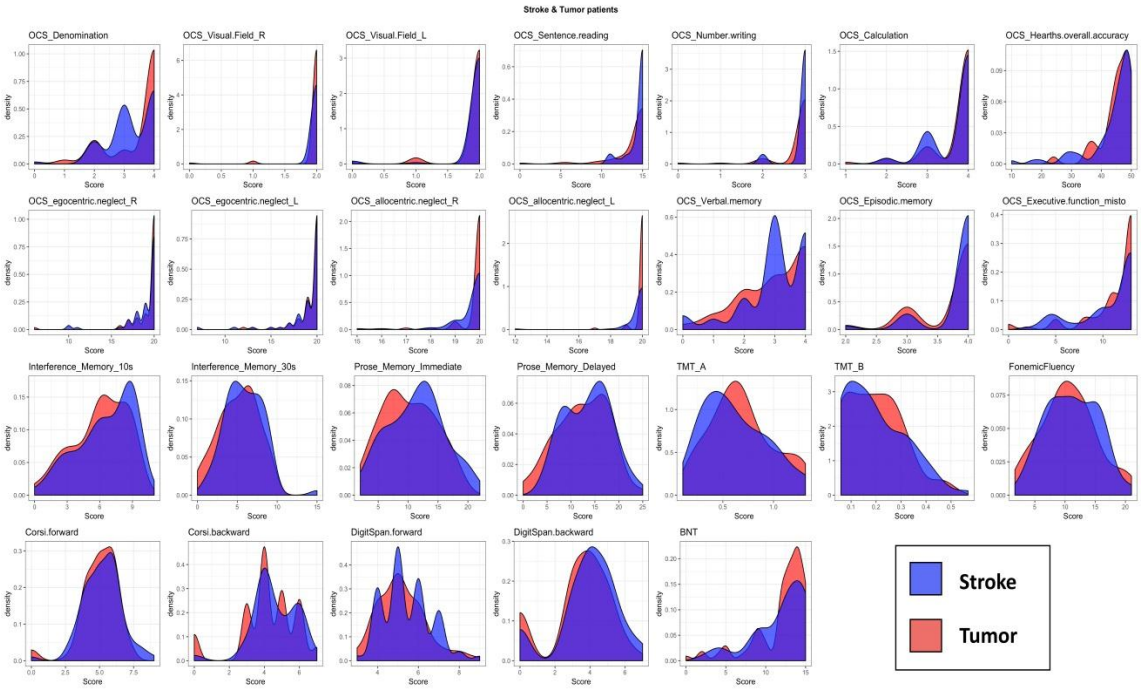


Fig. 6.2: Frequency distribution of cognitive performance. The frequency distributions of neuropsychological scores at each test are represented, both for tumor population (red area) and stroke population (blue area). High scores on the X-axis indicate more normal performance.

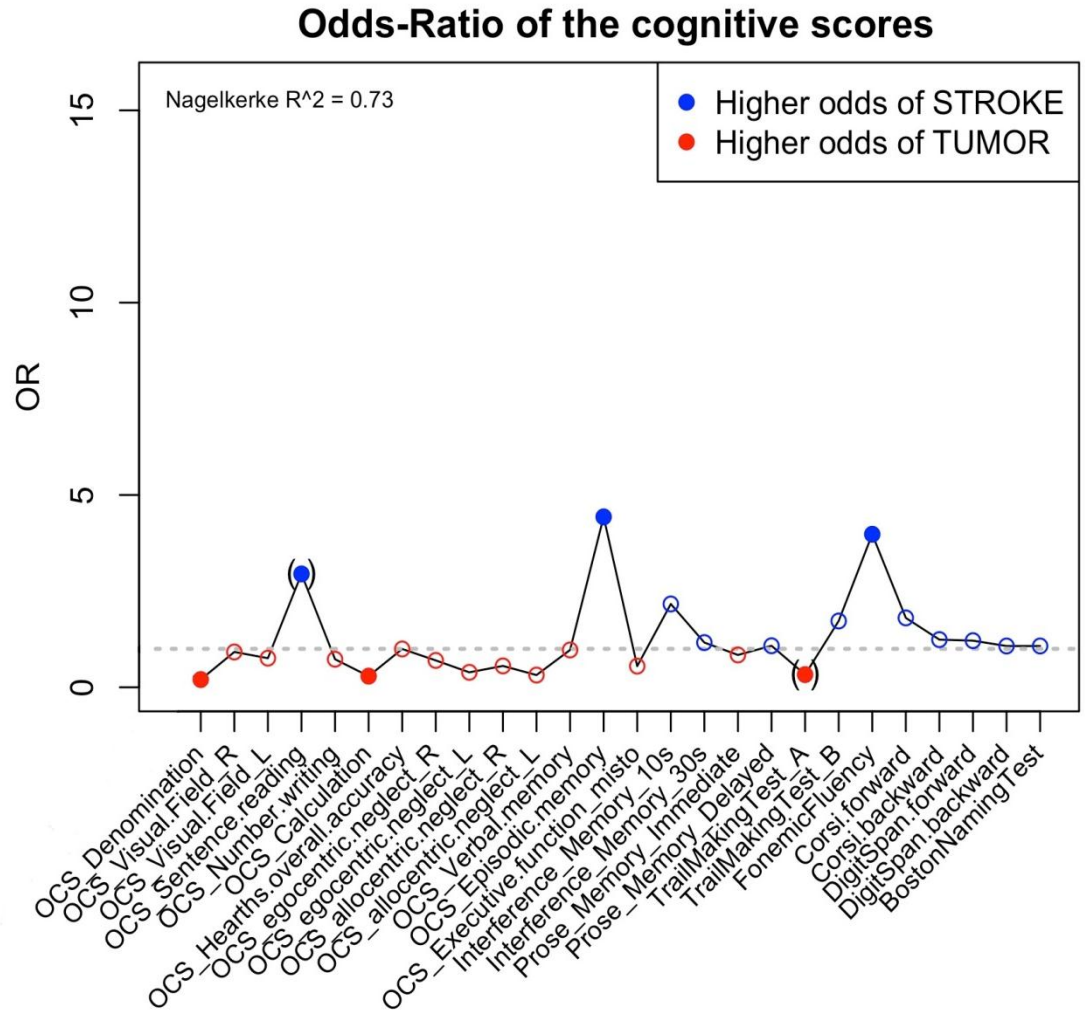


Fig. 6.3: Results of logistic regression. The Y-axis reported the odd ratio of each test (listed on the X-axis). Full dots indicate tests which significantly predicted the diagnosis, dots in brackets indicate tests with a tendency to significance. Performance in four tests significantly discriminated a patient with a tumor or stroke: high scores in denomination and calculation were more probable in patients with tumor, while high scores in episodic memory and phonemic fluency were more probable in patients with stroke. (R = right; L = left; OR = odd ratio; OCS = Oxford Cognitive Screen).

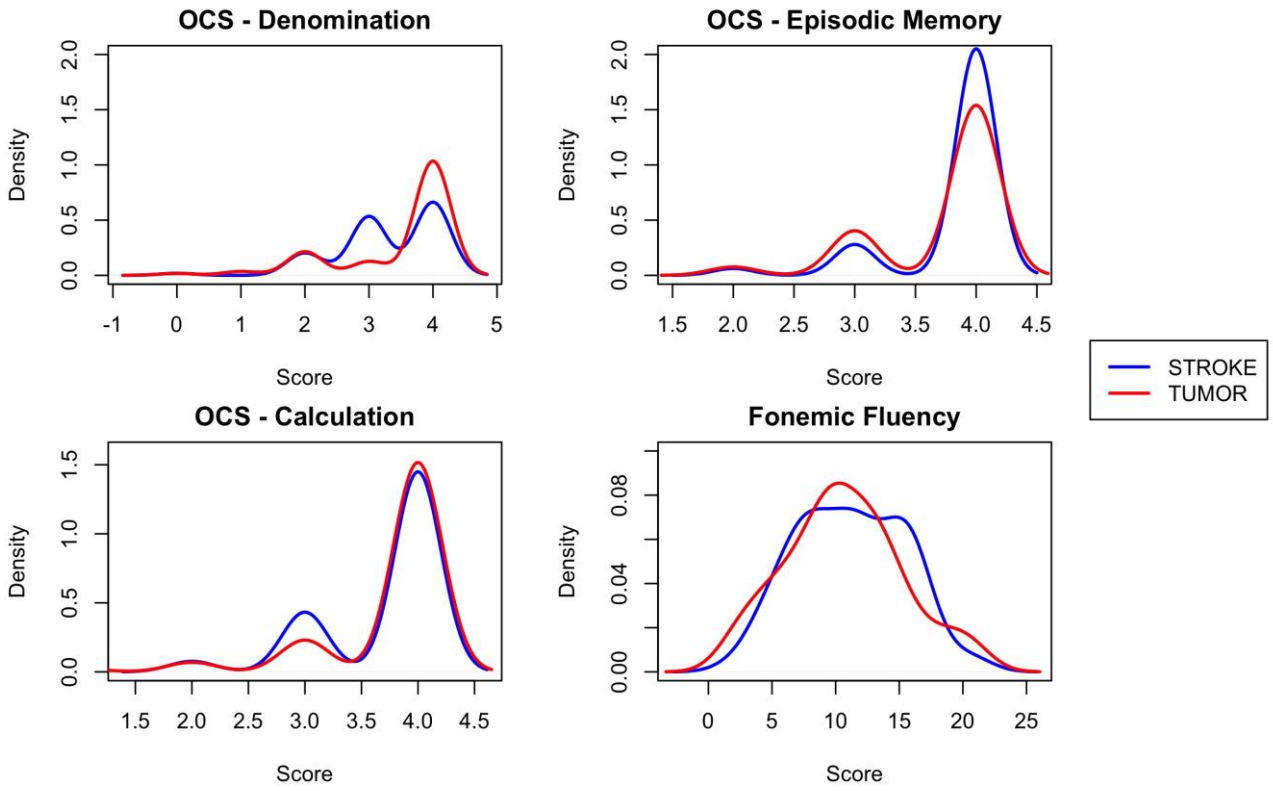


Fig. 6.4: Frequency distribution of the four tests significant in the logistic regression, in the two sample of patients. High scores on the X-axis indicate more normal performance

Lesion anatomy

To compare tumor and stroke lesion topographies, a voxel-wise analysis was implemented. By overlapping all lesions, frequency maps of the same slices were created. Tumor lesions occurred prevalently in frontal and temporal cortex, specifically at the white-gray matter junction, with a more heterogeneous distribution. Indeed, less than 20% of patients had a lesion in the same location (Fig. 6.5).

Stroke lesions were more common subcortically especially in the basal ganglia and central white matter (Fig. 6.6).

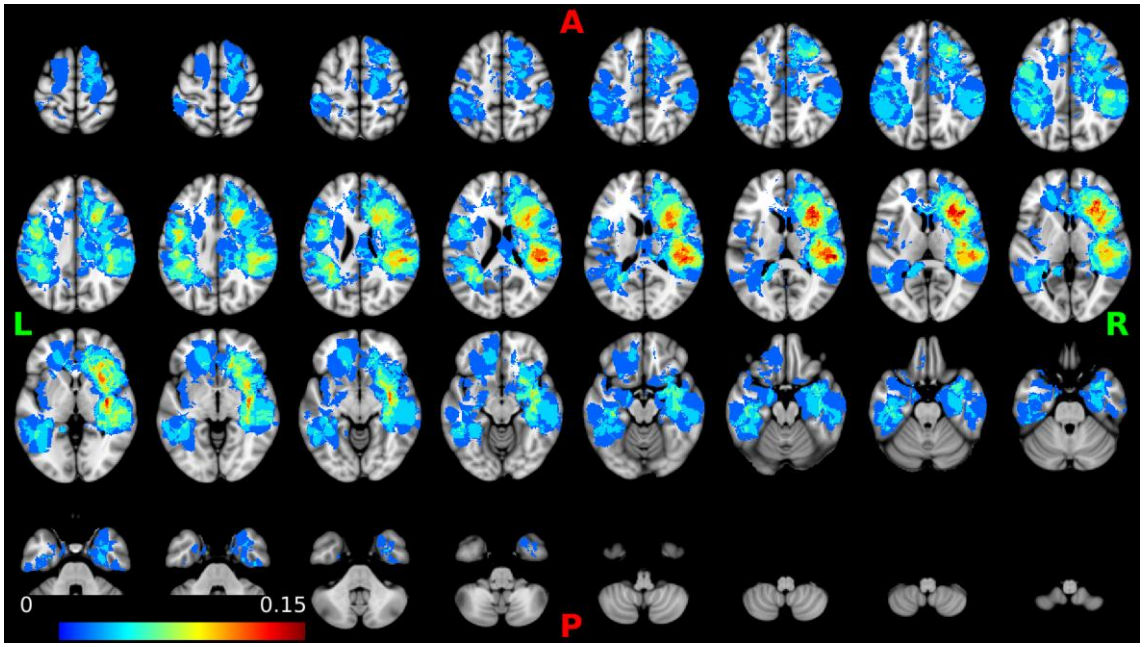


Fig. 6.5: Tumor lesion frequency map. The red color indicates higher overlap between lesions. The lesions occurred prevalently in frontal and temporal cortex, specifically at the white-gray matter junction, with an heterogeneous distribution. Indeed, less than 20% of patients had a lesion in the same location.

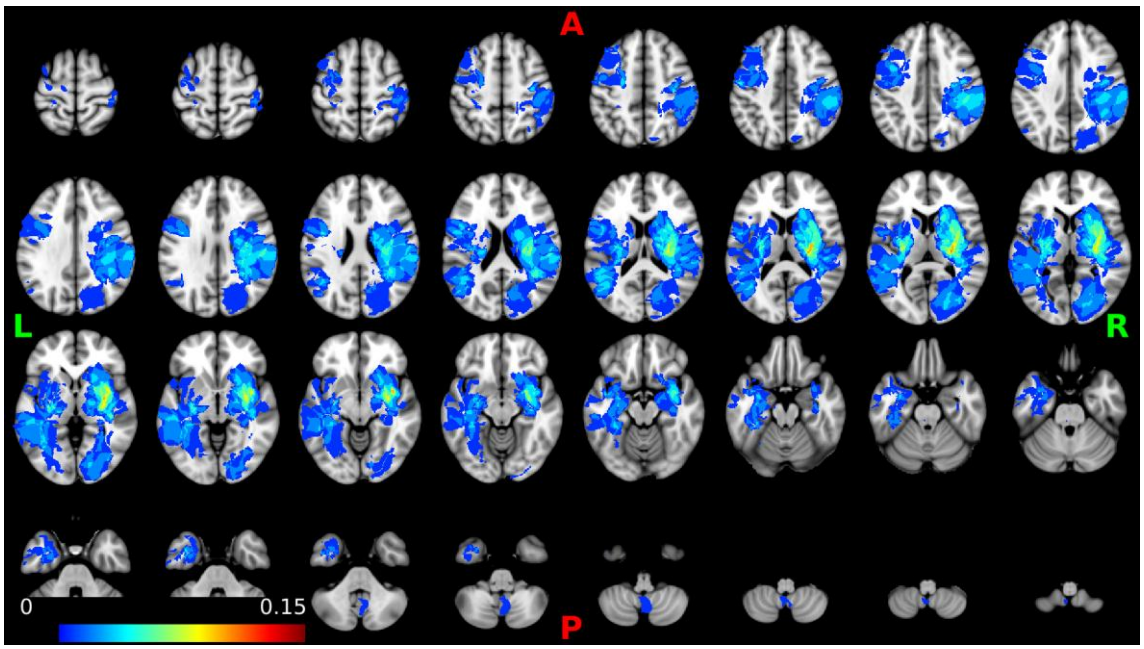


Fig. 6.6: Stroke lesion frequency map. The red color indicates higher overlap between lesions. The lesions were more common subcortically, especially in the basal ganglia and central white matter.

6.5 Discussion

Several studies have been conducted to characterize the consequences of brain tumors on cognitive functions. However, no study has defined thus far the profile of cognitive deficits in brain tumors while taking into account the specific neurological nature of this pathology and the effect of surgery. In general, stroke and tumors cause different pattern of cognitive impairment. A low dimensional set of behavioral impairments was found not only in stroke but also in tumor, and the correlation between deficits was similar between the two diseases, despite their different topography, at least for the two first PCs. This suggests that the mechanism of disconnection and remote dysfunction is partly independent of the kind of focal damage, whether it is acute or slow-growing. The small number of factors founded in both groups is consistent with a few behavioral clusters common across many subjects and the correlation founded between deficits is highly similar between tumors and stroke.

Whether one calls it network disruption or connectional diaschisis, the point is that focal damage can impair cognitive functions at a global level. Thus, if a specific network/white matter tract is interrupted in one point, the functional disconnection might be the same whether the focal damage is acute, as in stroke, or chronic, as in tumor. The fact that in slow growing lesions there is time for compensation and network reorganization probably explains why impairments are different respect to acute injury. As argued in Corbetta et al. (2015), the identification of a reduced number of factors of behavioral deficits in a neurological syndrome is clinically important, because allows shifting the focus of the clinician from the rare and interesting cases to the great majority of patients without a specific behavioral syndrome. This is especially true in the case of brain tumors, where the manifestation of symptoms is more subtle.

The lesion topography in the two samples was quite different: tumors affected the gray-white matter junction and their distribution was more variable in frontal and temporal cortices. Strokes were mainly localized in subcortical white matter and basal ganglia with about 10-15% affecting the cortex. Basal ganglia are more often interested due to the more frequent median cerebral artery involvement. As for brain tumors, meningiomas primarily compress cortical tissue, and intracerebral neoplasms have been

reported to also interest mainly cortical areas. Hence, both samples were representative of their respective usual populations.

In addition, we tried to find a method to differentiate between tumor and stroke from the cognitive profile. More precisely, we investigated if starting from a specific cognitive profile, it was possible to determine whether the subject had a stroke or a tumor. The results show that, although both groups of patients display similar deficits, each pathology is characterized by a specific cognitive profile. The model found the following specific tests as a good discriminative tool between brain tumors and stroke: a worse performance in denomination and calculation subtests of OCS were discriminative for stroke, while a worse performance in episodic memory (subtest OCS) and phonemic fluency were discriminative for brain tumors. These differences may be related to the more local vs. distributed nature of stroke vs. tumor damage, respectively. Calculation and denomination may be more dependent on specific brain regions, while episodic memory relies on more distributed sets of regions. In conclusion, we found a more specific characterization of the cognitive profile of the two pathologies. In the future, it will be useful to validate the model on another sample of patients with brain tumor or stroke.

6.6 Conclusions

In conclusion, mild acute strokes and brain tumors generally cause different patterns of cognitive impairment; however, the correlation between deficits is similar between the two diseases, despite their different topography. This is an important finding, because it implies that not only acute injury, as found by Corbetta et al. (2015), but also slow-growing lesions cause a low-dimensional set of behavioral impairments. These behavioral phenotypes are therefore robust to recovery in stroke (Ramsey et al., 2017), behavioral assessment (Corbetta et al., 2015) and etiology (stroke vs. tumors). In other words, the fact that the correlation between deficits was similar in stroke and tumors, despite their different topography, indicates that lesion location alone is not able to predict behavioral impairment, but that once again there must exists a common (physiological) mechanism that disrupts normal brain functioning. We postulate that

low dimensional alterations in structural and functional connectivity may explain this similarity in behavior.

The results also show that although both groups of patients display similar deficits, each pathology is characterized by a specific cognitive profile. Specifically, brain tumor patients tend to have fewer sensory, motor, or language deficits, and more memory, executive, and attention deficits. Therefore, high level cognitive deficits are those we shall focus on when evaluating brain tumor patients pre- and post-surgery. This issue emphasizes the necessity of an even more suitable neuropsychological battery, able to detect the subtle cognitive deficits consequent to brain tumors, comparing to other neurological pathology with different physiological process beneath (i.e., focal epilepsy).

Further investigations should compare the relationships between lesion location and volume and behavioral PCs in the two diseases. For example, an interesting approach would be to compare the dysconnectome patterns that can be derived from the different lesion distribution as in the work of Thiebaut de Schotten and Foulon (2018).

Part 4: Longitudinal study

Chapter 7

Study 3
Longitudinal study on effect of the treatment on cognitive functions

7.1 Background

In the previous study we defined the cognitive profile of brain tumors using principal component analysis. The second question concerns the impact of the surgery on cognitive functions. Several studies have been conducted to quantify in the long term the impact of surgical procedure on cognitive abilities. Some studies reported acute cognitive deficits after surgical resection, while others showed no effects. This variability depends on the time at which the follow-up is scheduled. Talacchi et al. (2011) administered an extensive battery of neuropsychological tests, which explored different cognitive domains, to 29 patients before and after surgical removal of their cerebral glioma. More than 50% of the patients had a deficit in verbal and/or visuo-spatial episodic memory. In this study, only the cumulative score on the episodic memory tests significantly improved from the pre to the post-operative period. Effect of the surgical resection on cognition have been studied extensively also in meningiomas. A recent review shows that meningiomas cause cognitive deficits in the majority of patients, but the surgery leads to an immediate recovery of this impairment (Rijnen et al., 2019), whereas some studies reported an improvement in cognitive functions in the long term (Tucha et al., 2003).

From a clinical point of view, it would be interesting to identify the pre-surgical variables that are predictive of the cognitive trend after the resection. Dallabona et al. (2017) gain some important results in this direction, by investigating the pattern of pre-

surgical variables determinant in predicting the cognitive performance of the patients after neurosurgery, including both demographic and clinical features, such as patient age, tumor location, mass effect and effects of surrounding edema. A combination of age, tumor mass effect and lateralization was found to be a good predictor of the cognitive performance in the follow up. More specifically, the recovery at one month after surgery was associated with a lower age and a smaller overall mass effect.

7.2 Aim of the study

The aim of this study is to evaluate the effects of the surgery on cognitive functions in the long term, taking into account the dimensionality of cognitive deficits. To achieve this goal, we applied the method used by Corbetta et al. (2018) to study the cognitive re-organization of stroke patients during different follow-up periods. This study found a stability of the components at 3 and 12 months after the event. This suggests that, at the population level, stroke lesions commonly cause a low dimensional set of behavioral deficits, which seemingly reflect a correlation of physiological processes that are represented in a distributed network rather than in local modules.

We focused on studying how the components found in the previous study changed after the surgery and during, at different time point since the resection, in order to investigate if the surgery is responsible for a reorganization of cognitive system.

7.3 Materials and Methods

Sample

Fifty-one of the 80 patients composing the total sample underwent one-month follow up. The specific inclusion criterion in this study was the eligibility to the surgical resection. The reasons of the drop-out were the following: no surgical indication (n=5); death (n=3); logistic problems (n=7); refusal to come to visit (n=3); transfer to rehabilitative structure (n=6); exacerbation of medical problems (n=5). The sample was equally distributed for gender (M=26; F=25); mean age was 58.9 years (range: 36-83). According to the histopathological exam the patients had gliomas (high grade=33; low grade=4) and meningiomas (n=14). The lateralization of the lesion was equally

distributed in the sample (left=28; right=23). All the enrolled patients underwent resection (Table 7.1).

Histology	**n.**	**Age (mean)**	**Education (mean)**	**Gender (M/F)**
High grade gliomas	33	60	10.7	21/12
Low grade gliomas	4	45	11.7	2/2
Meningiomas	14	60.4	9.3	3/11

Table 7.1: demographic characteristics of the sample, divided for etiology.

Neuropsychological assessment

The neuropsychological assessment was performed in the week before surgery (T1), in the week after surgery (T2) and one month after surgery, before the pharmacological treatment (T3).

Statistical analysis

Preliminarily, neuropsychological scores were scaled and mean centered on T1 mean, then dimensionality reduction was performed on the behavioral data using principal component analysis, on T1, T2 and T3 neuropsychological data.

A mixed-effects linear regression model was run to test the influence of age, gender, education, histology and time (T1, T2, T3) on cognitive tests score. We also considered in the model the interaction between histology and time. The OCS subtests Semantic and Orientation were not considered in this analysis because performance of the whole sample obtained on these tests was too high (i.e., the maximum score). In order to obtain the same scale for each test, we transformed the time of execution score in the TMT test and the PEG test in a correct item per second measure.

7.4 Results

Effects of surgical resection

PCA was repeated on the behavioral data at each of the three different time points separately (Fig 7.1). The PCA on T1 was previously described (see study 1), and revealed three main factors (PC) explaining 50% of T1 cognitive performance: PC1 mainly loaded on language and praxis; PC2 mainly loaded on visuospatial abilities and attention; while PC3 loaded on memory. The PCA on T2 revealed three main factors explaining 50% of cognitive performance: PC1 (29%) mainly loaded on language and memory; PC2 (11%) mainly loaded on executive functions and manual dexterity; while PC3 (10%) loaded on orientation, praxis and visual field. The PCA on T3 revealed three main factors explaining 54% of cognitive performance: PC1 (34%) mainly loaded on right visual field, praxis, and number writing; PC2 (11%) mainly loaded on executive functions; while PC3 (9%) loaded on denomination, reading, phonemic fluency and digit span (Table 7.2).

In the mixed regression model (Fig. 7.2), we found significant effects of age (χ^2 (1)=27.9; p<0.001) and time (χ^2 (2)=41.7; p<0.001) on the cognitive performance. An increase in age was associated with general worse cognitive performance. Interestingly, the interaction between time and histology (high, low grade, meningiomas) was also significant (χ^2(4)=10.3; p=0.03), revealing a different effect of neurosurgery on neuropsychological performance depending on the different types of tumor.

Post-hoc contrasts on the time main effect revealed a global worsening of cognitive scores on T2 (z=2.5; p<0.001), with subsequent recovery at one-month follow-up (z=-4.3; p<0.001). The analysis was repeated considering the interaction between histology and time. High grade gliomas showed significantly worse performance from T1 to T2 (z=5.5; p<0.001), and recovery from T2 to T3 (z=-3.9; p<0.001). Meningiomas showed the same trend: a decline from T1 to T2 (z=1.6; p<0.001) and an improvement from T2 to T3 (z=-4.07; p<0.001). There were no significant differences in low grade gliomas between T1 and T2, but an improvement between T2 and T3 (z=-1.4; p<0.001).

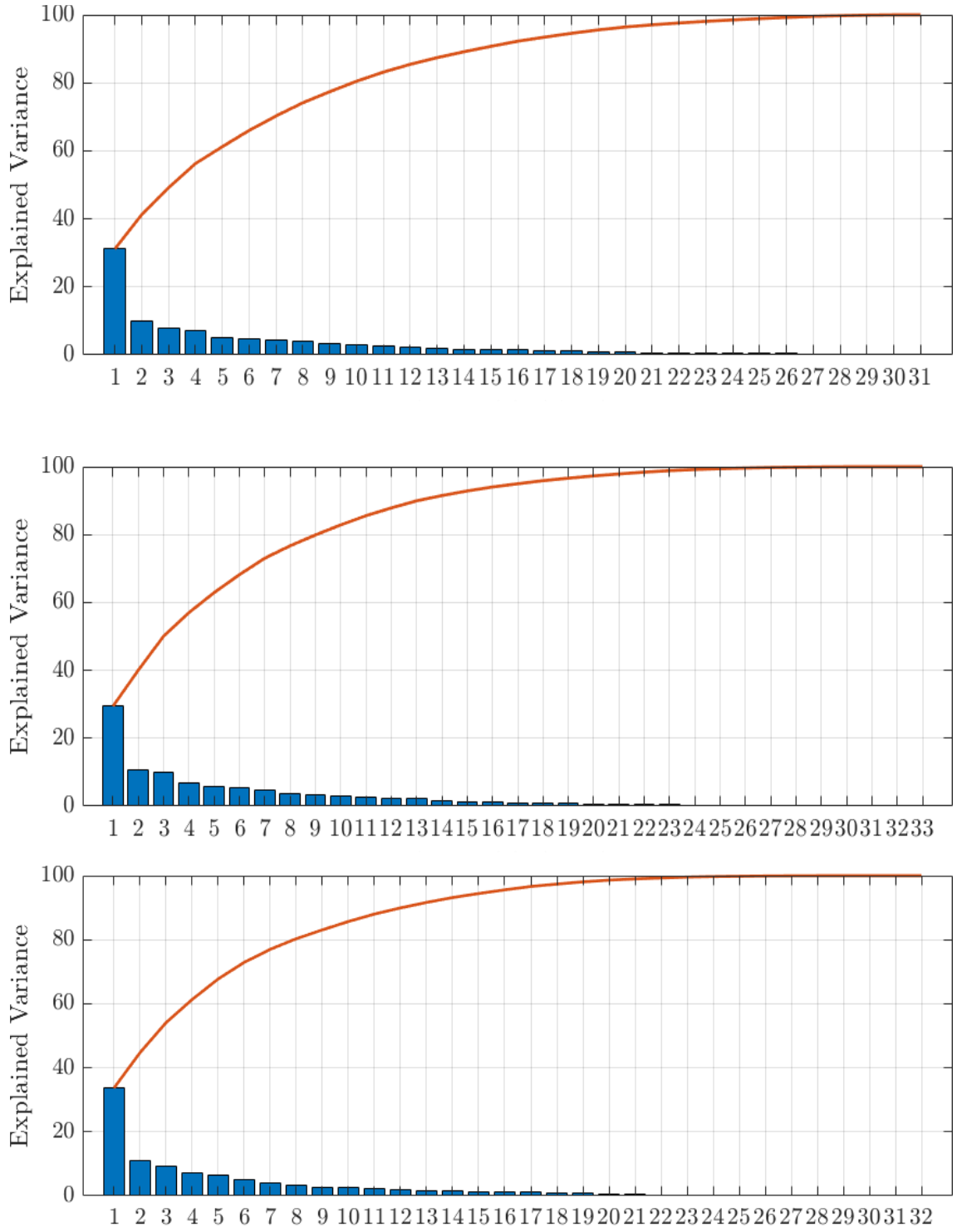


Fig. 7.1: Screening plots of explained variance at the three different time points (respectively: pre-surgery, post-surgery, 1 month follow up). The red line represents the sum of the percentages of the variance explained by the components.

	Pre – surgery (T1)			Post – surgery (T2)			1 month follow up (T3)		
Test	**PC 1**	**PC 2**	**PC 3**	**PC 1**	**PC 2**	**PC 3**	**PC 1**	**PC 2**	**PC 3**
OCS-Denomination	-0.2		0.2	0.3					-0.4
OCS-Orientation						0.5			
OCS-Visual Field-Right			0.2			0.5	0.4		
OCS-Visual Field-Left									
OCS-Sentence reading	-0.4			0.3					-0.3
OCS-Number writing	-0.4				-0.3		0.4		
OCS-Calculation	-0.3				-0.2			0.4	
OCS-Hearths overall accuracy		0.3							-0.2
OCS-egocentric neglect-Right	-0.2	-0.2				0.2	0.2		0.3
OCS-egocentric neglect-Left		-0.3	0.2			-0.3		-0.2	-0.2
OCS-Imitating gesture-Right	-0.4					0.3	0.4		
OCS-Imitating gesture-Left	-0.4					0.3	0.3		
OCS-Verbal memory			0.3	0.3			0.4		
OCS-Episodic memory			0.2				0.3		
OCS-Executive function-simple		0.4			-0.3			0.4	
OCS-Executive function-mixed		0.3			-0.4			0.5	
OCS-Executive function-total	0.2	-0.2			0.3	-0.2		-0.5	-0.2
Memory Interference-10s			0.3	0.3					-0.2
Memory Interference-30s			0.4	0.2				0.2	-0.2
Prose Memory-Imediate			0.3	0.3				0.2	
Prose Memory-Delay			0.4	0.3					-0.2
TMT-A		-0.3		-0.2			-0.3		
TMT-B		-0.2		-0.2					
Phonemic Fluency			0.2	0.2	-0.2				-0.3
Corsi test forward		0.3			-0.3				
Corsi test backward		0.3			-0.3			0.2	
Digit Span forward			0.2	0.2		-0.2			-0.3
Digit Span backward			0.2	0.3			-0.2		-0.4
Boston Naming Test			0.2	0.4	0.2				-0.3
PEG-right hand	0.2				0.3	0.2			0.2
PEG-left hand		-0.2			0.4		-0.2		

Table 7.2: Loading on the first three PCs at the three different time points.

Post-hoc contrasts on the interaction between histology and session revealed a significant difference in cognitive performance only between high grade gliomas and meningiomas at T3 (z=-2.9; p=0.008), while other contrasts were not significant.

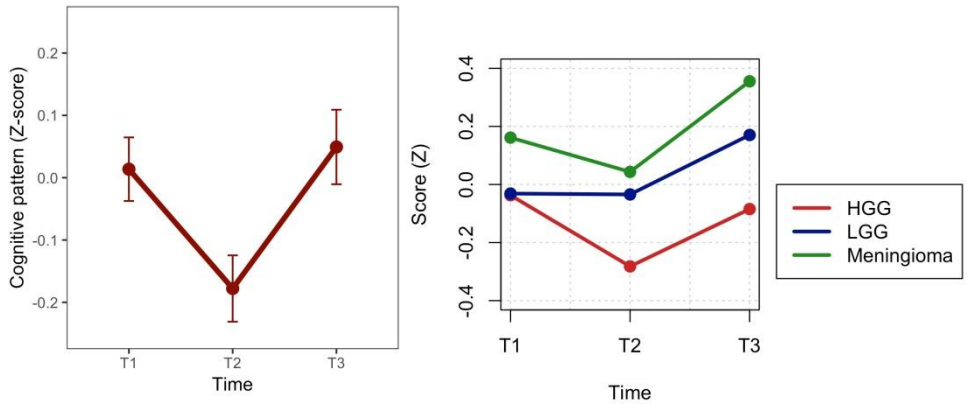


Fig. 7.2: the trend of cognitive performance through the different time points: (T1) pre-surgery; (T2) post-surgery); (T3) 1 month follow up.

Effects of treatment (radiotherapy and chemotherapy)

Although only a very small number of patients (n=30) have been enrolled so far after 4 months (after pharmacological treatment), we conducted a preliminary analysis on this sample with the aim of evaluating the interaction between surgery and treatment on cognitive functions. More specifically, we repeated the same analysis described above, by including the T4 in the model. Demographic characteristics of the sample are summarized in Table 7.3. The total mean age was 57 years old (range 36-83) and the mean years of education were 10,6 (range 2-18). The sample included gliomas (high grade=17, low grade=4) and meningiomas (n=9). The sample was also well balanced for gender (M=14; F=16). 14 patients were lost after T3, while the protocol is still ongoing for 5 patients. The reasons of the drop-out were the following: exacerbation of medical conditions (n=5); refusal to come to visit (n=4); onset of other medical conditions (n=4); death (n=1).

Histology	n.	Age (mean)	Education (mean)	Gender (M/F)
High grade gliomas	17	57	11	11/6
Low grade gliomas	4	45	11.7	2/2
Meningiomas	9	61.8	9.3	1/8

Table 7.3: demographic characteristics of the sample that underwent pharmacological treatment, divided for etiology.

All the 17 patients with high grade glioma underwent treatment with radiotherapy and chemotherapy. The radiotherapy lasted from 4 to 6 weeks. The patients were also treated with Temozolamide. Patients with low grade glioma and meningioma did not take any therapy.

In the mixed regression model, age (χ^2 (1)=27.5; p<0.001) and time (χ^2 (2)=49.6; p<0.001) still had significant effects on the cognitive performance. The post-hoc contrasts revealed a significant difference in performance between T2 and T4 (z=-3.8; p<0.001), but not between T3 and T4 (Fig. 7.3).

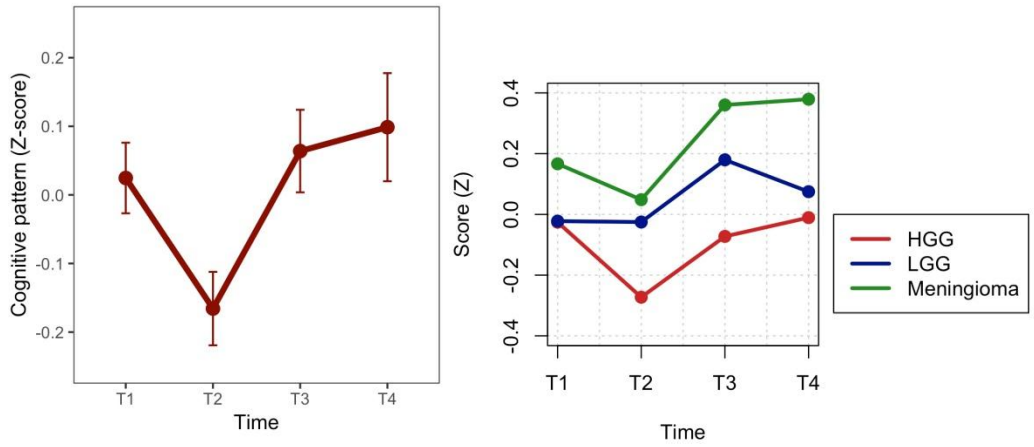


Fig. 7.3: the trend of cognitive performance through the different time points: (T1) pre-surgery; (T2) post-surgery); (T3) 1 month follow up; (T4) 4 months follow up.

7.5 Discussion

The principal components analysis conducted across different time points revealed a different combination of cognitive domains that explained the general cognitive profile. These results may suggest a reorganization of the cognitive system in patients after tumor resection, if compared to the cognitive impairment due to the tumor itself. Specifically, in the immediate post-operative stage we found impairment on a wider range of domains, including language, attention and memory, which explained the global cognitive damage. This result is in line with the observation of a general worsening of performance in the immediate post-operative stage as compared to the pre-operative performance.

The analysis on the trend of the cognitive performance through different time points suggests that the surgery has an impact on cognitive functions in patients with brain tumors only in an immediate post-operative stage, but the follow-up assessment might disclose a spontaneous recovery to pre-operative functioning, without rehabilitation. In other words, surgical treatment in itself seems to have little long-time disruptive effects on cognition. From a physiological point of view, the cognitive recovery may be explained by a reduction of the mass effect as time passes by the surgery. Despite the small sample size, we found a significant difference between high grade gliomas and meningiomas in the cognitive performance at one month follow up, suggesting a global higher improvement in patients with meningiomas. This long-term result may reveal a different way to react to surgery, despite the similar trend of improvement. The explanation could be due again to the different pathophysiological behavior in affecting brain tissue (Campanella et al., 2018).

The results just described are in agreement with previous studies that found a recovery at long-term follow up. Remarkably, for the first time in the literature, we tried to conduct a unique study in which the trends after surgery of tumor of different histology (gliomas and meningiomas) were directly compared. Some studies have already investigated the impact of tumor resection on cognition, however they considered only one etiology (Habets et al., 2014; Meskal et al., 2016; Dallabona et al., 2017; Campanella et al., 2017; Rijnen et al., 2019) or, when conducted on different types of tumors, they were focused on one specific cognitive function (Cipolotti et al.,

2015; Campanella et al., 2015; Campanella et al., 2018). In our sample, we found that the most sensitive scores in predicting the effect of surgery were related to memory and attention. Therefore, to assess whether surgery had caused deficits, it is important to focus on these domains. Moreover, these functions are those which we shall focus on in the attempt to link neuropsychological deficits to biological variables of the tumor, or to examine mechanisms of recovery of function. A wider sample size is needed for a better comprehension of the interaction between the different pathophysiology of different type of tumors and the surgical procedure adopted by neurosurgeons, in predicting the cognitive consequences in the long term. Identifying the pre-surgical factors that may predict the post-surgical recovery could have clinical relevance in term of a better planning of the surgical procedure and the rehabilitative treatment.

Concerning the effect on cognition of radiotherapy and/or chemotherapy, a wider sample of patients treated is also needed to better understand the effect of the treatment on cognition. The challenge is to identify the pre-surgical demographic, anatomical and cognitive variables that allow predicting the cases that are more vulnerable to the effect of the treatment, from a neuropsychological point of view.

Chapter 8

Study 4
PET/RM study

8.1 Background

MRI is the most widely available methodology to study brain tumors, but has a number of limitations concerning grading and definition of the real extent of the pathology. PET/CT that is used for tumor grading has limited spatial resolution, but the capacity of characterizing many molecular aspects of the pathology. Using an integrated 3T PET/MRI system, able to simultaneously acquire dynamic PET and MRI images, enabled us to integrate the advantages of both methodologies with the possibility of detecting simultaneously structural changes (morphologic sequences and DTI), basal functional changes (BOLD default mode network), functional activation changes (AS labeling, BOLD task positive network) and changes in metabolic rate of glucose pre- and post-surgery, and to correlate these measures with behavioral outcomes (Cecchin et al., 2017).

Tumors/resections affecting the white matter, especially regions of convergence of many white matter tracts, will lead to more severe cognitive deficits than tumors/resection affecting the cortex. Gliomas, as they extend in the white matter, may cause deficits of communication between brain regions that support associative functions (e.g. memory, attention, executive functions), rather than more localized sensory, motor, or language functions. This is consistent with our recent observation in stroke. Damage to the white matter was associated with deficits in multiple domains as compared to more specific deficits after cortical damage. Moreover, cognitive deficits are much less dependent on damage of specific cortical regions, but more dependent on the functional integration between brain regions (Siegel et al. 2016). As a result,

functional connectivity measures, rather than structural measures, are more related to cognitive outcome.

8.2 Aim of the study

The main hypothesis of the project is that 3T brain PET/MRI using absolute quantification of glucose and a complete set of functional, structural and anatomical sequences will allow a complete mapping of the areas suffering from brain tumor locally or through dysconnection, thus allowing a much better surgical planning, prediction of the outcome, a precise and quantitative monitoring of the effect of therapies. Finally, these data will help understanding post-surgical neuronal remodeling. We measured the tumor and its effects on the brain's structural and functional organization by acquiring:

- structural data about the lesion (e.g., volume, edema, shape)
- distortion of structural connectivity measured with DTI
- alterations of functional connectivity measured with R-fMRI

All these imaging measures will be correlated with behavioral data collecting at the same time points.

8.3 Materials and methods

Patient of at least 18 years of age, planned for surgical removal of a brain tumor were enrolled. Simultaneous PET/MRI scans were acquired pre-surgically at the Nuclear Medicine Unit, Department of Medicine – University Hospital of Padova, on a Siemens Biograph mMR (Siemens Medical Solutions USA). A 70 min of 18F-FDG positron emission tomography imaging was acquired, starting immediately before the radiopharmaceutical administration. The MR brain imaging protocol included the following sequences:

- T1
- T2-weighted
- T2-weighted Fluid Attenuate Inversion Recovery (FLAIR)
- Diffusion tensor imaging (DTI)
- Resting state functional MRI (fMRI)

Patients will be then surgically treated. Post-surgery (1 month), the same diagnostic protocol will be performed to quantify surgically related variations. At 4 months post-surgery, after radiotherapy and chemotherapy, the same protocol will be performed to assess functional, metabolic, and structural variations related to treatments.

Sample

This study is still ongoing. So far, we have enrolled 26 patients with high grade glioma (n=22) and low grade glioma (n=4). Currently, the sample is equally distributed for gender (M=14; F=12); mean age is 59.5 years (range: 25-83), the mean of education is 10.1 years (range: 2-18). Only one patient is left-handed. The specific histopathology is distributed as follows: glioblastoma (IDH1 wild-type: n=17; IDH1 mutant: n=1), astrocytoma (n=2), olygodendroglioma (n=3), others (n=3). Concomitant pharmacological treatment (anticonvulsive drug) is collected. The reasons of the drop-out through the longitudinal follow-up are described below (Fig. 8.1).

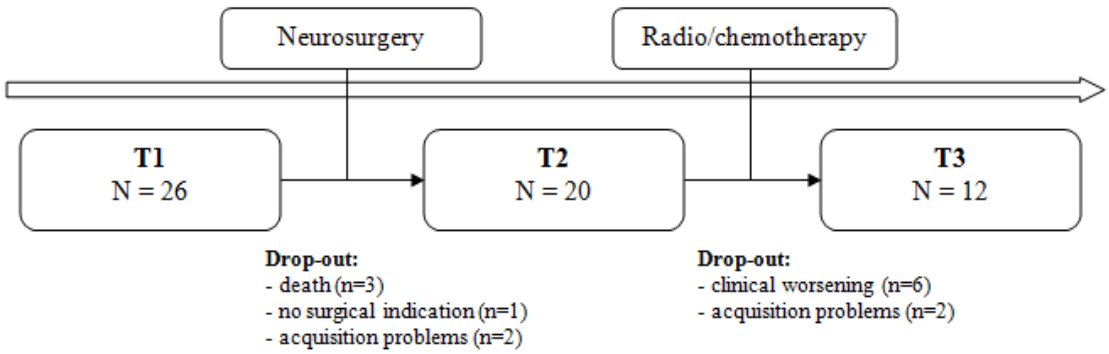


Fig 8.1: Number of patients enrolled so far at the different time points and the reasons of drop-out.

8.4 Expected results

The main outcome of this project will be an enhanced description of the behavioral deficits caused by tumors, and a more sensitive monitoring of the behavioral effects of surgery. The multi-modal neuroimaging pre-surgery may improve the surgical approach, and provide new information for the diagnosis of tumors, e.g. separating tumors with worse or better outcome. The comparison of multi-modal imaging features before and after surgery will provide novel information on the mechanisms of recovery of function.

The project is focused on the development of new multi-modal imaging in brain tumors, through the integration of PET/RM data with behavioral assessments longitudinally as a measure of the functional impact of the lesion, and as a possible new way to neuro-navigate the lesions prior to surgery. This study has strong clinical relevance to the practice of neurosurgery as it will clarify the biological effect of tumors on normal brain tissue and networks.

Conclusions and future perspectives

Clinical implications of the project

It is very important to define the cognitive profile of brain tumor patients, by identifying the pre-surgical risk factors that may predispose to secondary cognitive impairment of treatment. This is possible only with a complex model that includes demographic, anatomical, pathophysiological, and cognitive features and their interaction.

The clinical implications for better quality of life and planning cognitive rehabilitation are clear. The anatomo-clinical correlation has given us insight on the different distribution of cognitive abilities in the brain. This assessment identifies a precise cognitive profile, providing important diagnostic and prognostic information that can guide the following rehabilitation treatment.

This research has the potential to create a new approach for the diagnosis, outcome prediction, and surgical treatment of brain tumors. Specifically, the correlation of tumor variables and behavioral outcome with structural, functional, and metabolic metrics of brain organization may lead to more accurate diagnosis and long-term outcome prediction, as well as to the development of more accurate hence safer neuro-navigation of brain tumors.

Contribution to comprehension of brain architecture and plasticity

Brain tumors also represent a good model to study brain architecture and plasticity after damage, with implications for studies of recovery of function. Data in neuro-degenerative diseases in which cognitive function is maintained for a long time may suggest that the brain even in the adult state has strong potential for plasticity and reorganization after injuries. For instance, patients with Parkinson's disease show no behavioral deficits until the 80% of the dopaminergic cells of substantia nigra is destroyed (Desmurget et al., 2007). Further studies conducted by comparing brain tumors with other degenerative disease (focal epilepsy, Parkinson) could reveal in the future the mechanisms by which neuroplasticity works on brain tissue.

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